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One-Pot Transition Metal-Catalysed Processes for the Synthesis of Biologically Active Compounds

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A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

School of Chemistry

College of Science & Engineering

University of Glasgow

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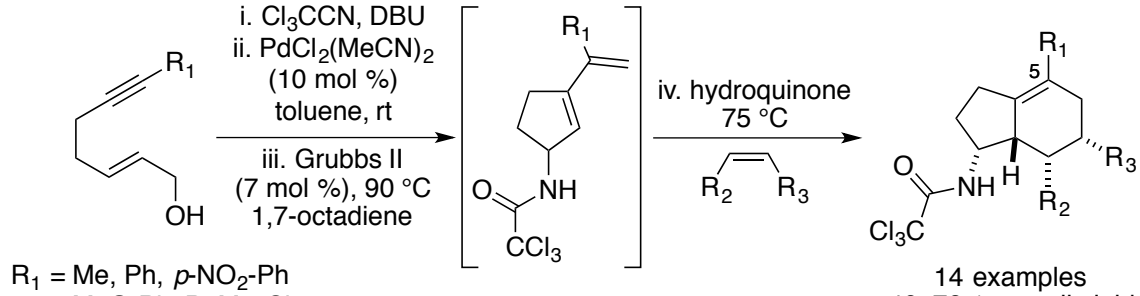
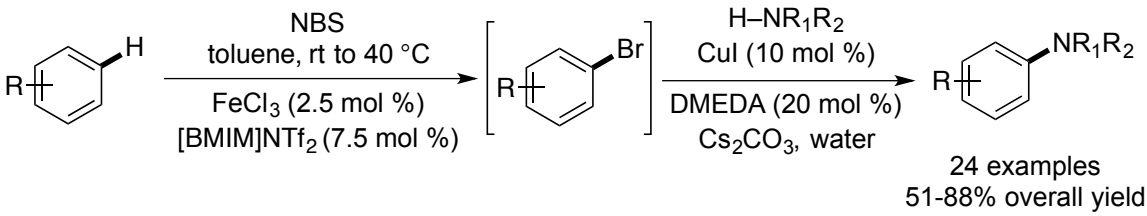
Abstract

The first section of this thesis describes the development of a one-pot Pd(II)-catalysed Overman rearrangement, Ru(II)-catalysed ring closing enyne metathesis reaction and a hydrogen bond-directed Diels-Alder reaction for the diastereoselective synthesis of C-5 substituted aminobicyclo[4.3.0]nonanes in good yields. To explore the late stage diversification of these compounds, further work investigated a one-pot synthesis of a benzyldimethylsilyl-derived analogue. The synthetic utility of this compound was demonstrated using C–C bond coupling reactions, for the late stage synthesis of a range of sp^3-rich bicyclononane scaffolds with up to six stereogenic centres.



The second section of this thesis describes the development of a one-pot two-step procedure for aryl C–H amination using iron and copper catalysis. Firstly, a mild and highly regioselective method for the bromination (and chlorination) of arenes *via* iron(III) triflimide activation of *N*-bromosuccinimide (or *N*-chlorosuccinimide) was developed. The scope of both processes was explored for the synthesis of a wide range of aromatic compounds and natural products. The one-pot iron(III)-catalysed bromination/Cu(I)-catalysed *N*-arylation was then studied. After optimisation, the one-pot two-step process allowed the synthesis of a large library of *para*-aminated aryl compounds in high yields as single regioisomers.



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Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis represents the original work of Mohamed A. B. Mostafa and has not been submitted for any other degree at the University of Glasgow or any other institution. The work upon which it is based was carried out at the University of Glasgow in the Loudon Laboratory under the supervision of Dr Andrew Sutherland between April 2014 and May 2017. Aspects of the work described herein have previously been published elsewhere as stated below.

M. A. B. Mostafa, M. W. Grafton, C. Wilson and A. Sutherland, *Org. Biomol. Chem*., 2016, **14**, 3284.

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M. A. B. Mostafa, R. M. Bowley, D. T. Racys, M. C. Henry and A. Sutherland, *J. Org. Chem*. 2017, **82**, 7529.

Signature _____

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Abbreviations

μW	Microwave
Δ	Reflux
Ac	Acetyl
Ar	Aromatic
BDMS	Benzyldimethylsilyl
BHT	Butylated hydroxytoluene (2,6-Di-*tert*-butyl-4-methylphenol)
BINAP	(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)
[BMIM]NTf_2	1-Butyl-3-methyl-imidazolium bis(trifluoromethylsulfonyl)imide
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broad
Bu	Butyl
°C	Degrees Centigrade
Cat.	Catalyst
Cbz	Carboxybenzyl
CI	Chemical Ionisation
Conc.	Concentrated
COP	Cobalt Oxazoline Palladacycle
COSY	Correlated Spectroscopy
Cy	Cyclohexyl

d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminium Hydride
DIP-Cl	(–)-Diisopinocamphenyl Chloroborane
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMEDA	*N*,*N'*-Dimethylethylenediamine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl Sulfoxide
dppf	Diphenylphosphinoferrocene
dr	Diastereomeric Ratio
EDG	Electron Donating Group
ee	Enantiomeric Excess
EI	Electron Ionisation
endo	Endocyclic
equiv.	Equivalents

er	Enantiomeric Ratio
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron Withdrawing Group
exo	Exocyclic
FOP	Ferrocenyl Oxazoline Palladacycle
g	Gram
h	Hour
Hex	Hexyl
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
IR	Infrared
LDA	Lithium Diisopropylamide
m-	*Meta*-
M	Molar
m-CPBA	*meta*-Chloroperbenzoic Acid
Me	Methyl
MEM	Methoxyethoxymethyl
mg	Milligrams
mL	Millilitres
mmol	Millimoles

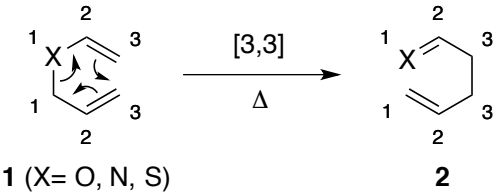
mol	Mole
mol. sieves	Molecular Sieves
MOM	Methoxymethyl
Mp	Melting Point
Ms	Methanesulfonyl
HMDS	bis(Trimethylsilyl)amide (Hexamethyldisilazide)
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
o-	*Ortho*-
p-	*Para*-
ppm	Parts Per Million
Ph	Phenyl
ppm	Parts Per Million
Pr	Propyl
Py	Pyridine
q	Quartet
quin	Quintet
RCEYM	Ring Closing Enyne Metathesis

RCM	Ring Closing Metathesis
ROM	Ring Opening Metathesis
rt	Room Temperature
s	Singlet
SET	Single Electron Transfer
SIPr.HCl	1,3-bis-(2,6-Diisopropylphenyl)imidazolinium Chloride
t	Triplet
TBAF	Tetrabutylammonium Fluoride
TBDMS	*tert*-Butyldimethyl Silyl
tert	Tertiary
Tf	Triflate
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	*N,N,N′,N′*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Tr	Triphenylmethyl
Ts	4-Toluenesulfonyl
XPhos	2-Dicyclohexylphosphino-2,4,6-triisopropylbiphenyl

1.0 Introduction

1.1 Claisen Rearrangement

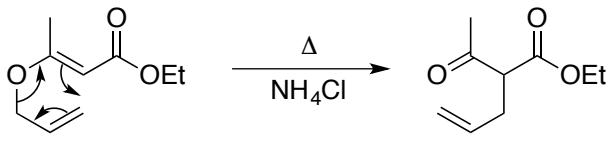
[3,3]-Sigmatropic rearrangements are a class of pericyclic reactions that possess a cyclic transition state in which bond-breaking and bond-making take place in one step. Among several types of sigmatropic rearrangements, the Claisen rearrangement, discovered by Ludwig Claisen in 1912,[1] has become a widely used reaction in synthetic organic chemistry.[2] This is due to its importance in the construction of a new carbon-carbon bond, as well as giving the desired products in high yields under relatively mild conditions. It is also especially useful because of the formation of a new carbonyl group as well as the generation of new stereocentres. The Claisen reaction was first defined as the “thermal isomerisation" of allyl vinyl ether **1** (when X = O) to form the γ,δ-unsaturated carbonyl product **2** (Scheme 1).[1,2]



1 (X= O, N, S) **2**

Scheme 1: A general Claisen rearrangement.

The first reported Claisen rearrangement described a thermal [3,3]-sigmatropic rearrangement of β-allyloxy-α,β-unsaturated ester **3** to form ethyl 2-allylacetoacetate (**4**) in the presence of ammonium chloride (Scheme 2).[1,2]

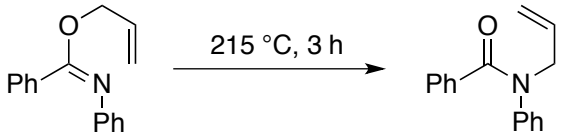


3 **4**

Scheme 2: The first reported Claisen rearrangement.

1.2 Overman rearrangement

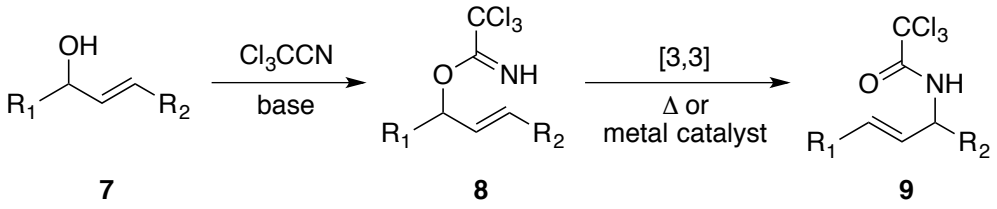
One important variant of this reaction is the aza-Claisen rearrangement, which involves the formation of protected allylic amines *via* a [3,3]-sigmatropic rearrangement of allylic imidates containing nitrogen and oxygen. This reaction was first discovered by Mumm and Möller in 1937, who investigated the rearrangement of the allylic benzimidate **5** to form the corresponding allylic benzamide **6** (Scheme 3).[3] However, this method has limited application in synthetic chemistry, due to low yields obtained for the formation of the allylic imidate substrates, and harsh conditions required for the [3,3]-rearrangement.[4]



5 **6**

Scheme 3: Aza-Claisen rearrangement of allylic benzimidate to allylic benzamide.

In 1974, Larry Overman reported the first [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates to corresponding allylic trichloroacetamides.[4] This transformation involves the reaction of allylic alcohol **7** with trichloroacetonitrile in the presence of catalytic amounts of base to form the allylic trichloroacetimidate **8**. This can be then directly converted to the allylic trichloroacetamide **9** through a [3,3]-sigmatropic rearrangement, which can be carried out either thermally or catalysed by transition metal complexes (known as the Overman rearrangement) (Scheme 4). Due to the ease of preparation of allylic trichloroacetimidates as well as the high yields obtained for the final allylic amide products, this process has become an attractive and useful methodology in synthetic organic chemistry. Moreover, removal of the trichloroacetyl-protecting group to form allylic amines would allow access to wide variety of nitrogen-containing products including natural products, amino acids, amino sugars, peptides, modified nucleotides and other *N*-heterocycles.[5]



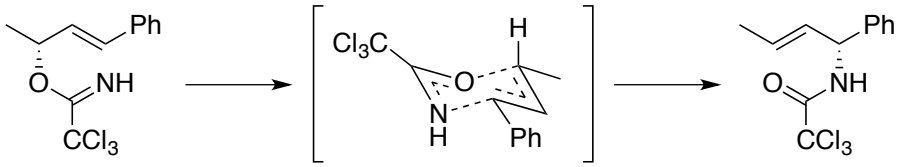
7 **8** **9**

Scheme 4: Overman rearrangement.

1.2.1 Thermal Overman Rearrangement

The Overman rearrangement can be carried out either thermally or catalysed by transition metals such as Hg(II) or Pd(II).[4,6] Under thermal conditions, the rearrangement is usually performed in solvents such as *p*-xylene at elevated temperatures.[4] Several studies have shown the broad scope of the thermal Overman rearrangement, in which the process can be applied to a wide range of primary, secondary and tertiary allylic alcohols. Temperatures required for these reactions are highly dependent on the structure of the imidates.[6] For example, the imidic esters of primary allylic alcohols can be isomerised at 140 ºC, while the tertiary imidates rearrange at 80 ºC.

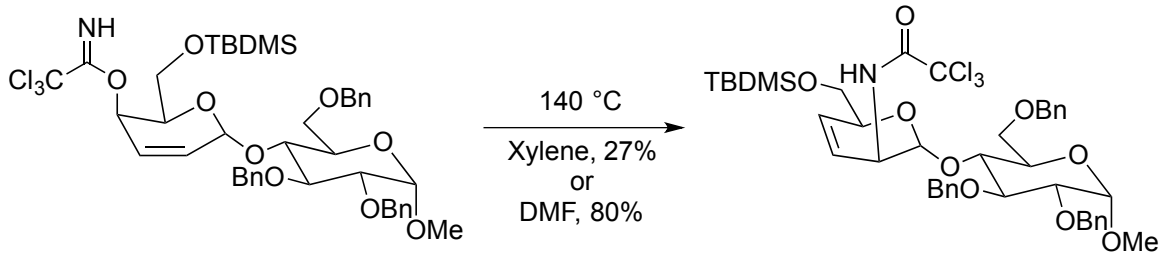
Similar to other pericyclic reactions, the [3,3]-sigmatropic rearrangement follows the Woodward-Hoffmann rules in which the rearrangement proceeds *via* a suprafacial process, thus it is thermally allowed.[7] As proposed by Shimoda and co-workers, the mechanism of this transformation proceeds *via* chair-type transition structure **11** in a concerted process, which means complete transfer of chirality from the allylic imidate to the allylic amide can be achieved.[8] In this process a new carbon-nitrogen bond is formed from the same face as the carbon-oxygen bond that is broken (Scheme 5).



10 **11** **12**

Scheme 5: Thermal Overman rearrangement.

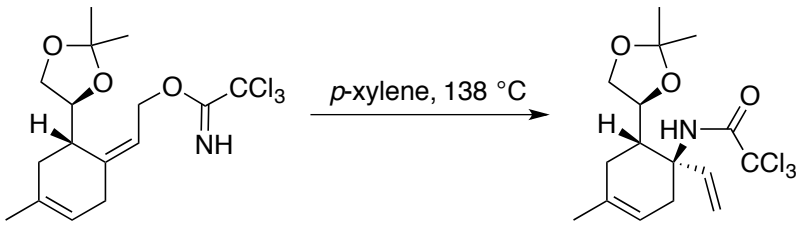
The rearrangement process is normally conducted in aprotic aromatic solvents such as xylene or toluene. However, more polar solvents such as DMF are preferred in some cases.[9] For example, the rearrangement of dissaccharide trichloroacetimidate **13** proceeded with 27% yield using xylene, whereas the yield dramatically increased to 80% when the reaction was carried out in DMF (Scheme 6).[9] The higher yield in this transformation is due to the use of DMF as a more polar and basic solvent which reduces the acid-catalysed decomposition of the imidate and enhances the reaction rate.



13 **14**

Scheme 6: Solvent effects on the yield of Overman rearrangement.

In 1998, Isobe and co-workers showed that the decomposition of the imidate could be avoided by adding small quantities of base to the reaction mixture.[10] They found that at high temperatures, the presence of small amounts of acidic by-products caused decomposition of the imidate starting material. This issue was avoided by adding a small quantity of potassium carbonate (2 mg/mL), resulting in an increase of yield (Scheme 7). Since then, these have become the most commonly used conditions for the thermal Overman rearrangement.

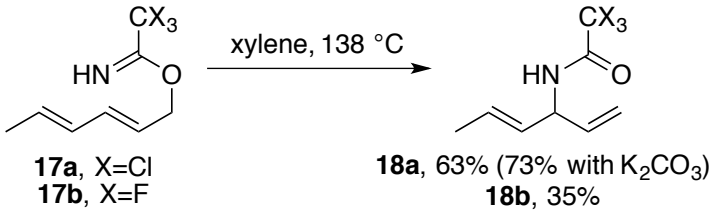


15 **16**

without K_2CO_3 (74% from allylic alcohol)
with K_2CO_3 (90% from allylic alcohol)

Scheme 7: Thermal Overman rearrangements of 15 with and without base.

The thermal Overman rearrangement can be influenced by the halogen substituent on the imidate. For example, the rearrangement of trichloroacetimidate analogue **17a** can provide the trichloroacetamide product **18a** in high yield, whereas a lower yield is observed for the trifluoroacetamide analogue **18b** (Scheme 8).[10,11] However, this is not always the case. In other examples, the trifluoro analogues can rearrange faster and more efficient than the trichloro derivatives.

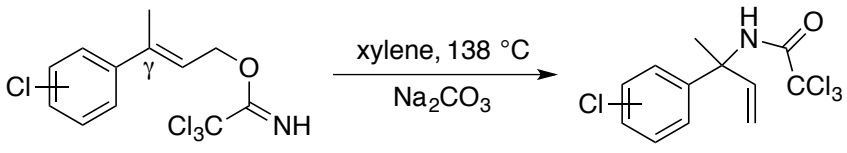


17a, X=Cl
17b, X=F

18a, 63% (73% with K_2CO_3)
18b, 35%

Scheme 8: Effects of halogen substituent on the thermal Overman rearrangement.

The presence of substituents on the gamma carbon of the imidate can play an important role on the thermal rearrangement. The example below shows the difference in yields between the rearrangements of *para*- and *ortho*-substituted aromatic trichloroacetimidates **19a**–**b** (Scheme 9).[12] While the *para*-substituted analogue rearranges to **20a** in 82% yield after 12 hours, the *ortho*-substituted amide **20b** is formed in a much lower yield (30%) and longer time (24 hours). The difference in reactivity between both reactions was due to steric hindrance effects between the γ-methyl group and the *ortho*-chlorine during rearrangement.



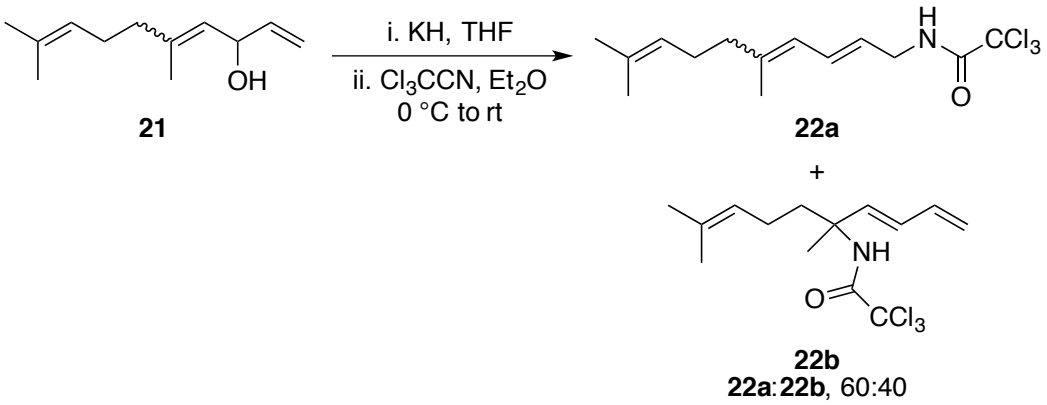
19a, *p*-Cl
19b, *o*-Cl

20a, 12 h, 82%
20b, 24 h, 30%

Scheme 9: Steric effects on the rearrangement of 19a–b.

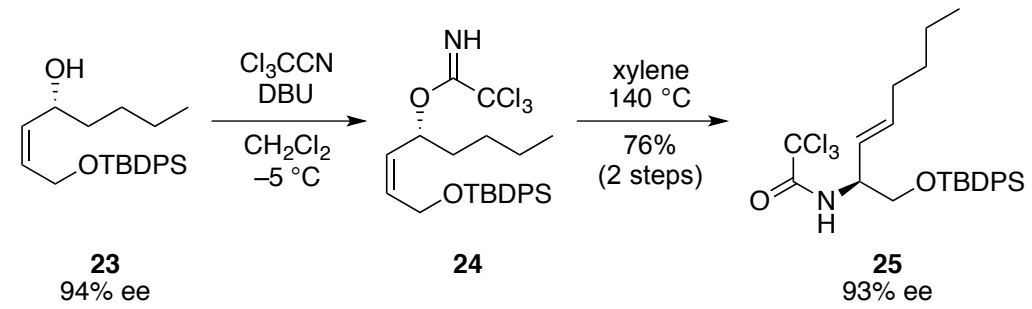
In terms of regioselectivity, the thermal rearrangement of an imidate having two different double bonds normally gives a mixture of two regioisomers. For example, the rearrangement of dienyl imidate derived from allylic alcohol **21** leads to a

mixture of both amides **22a** and **22b** in a ratio of 60:40 (Scheme 10).[6] The slight observed preference may due to faster rearrangement at the less hindered alkene.



Scheme 10: Regioselectivity in the Overman rearrangement.

The use of the [3,3]-sigmatropic rearrangement is especially important because it allows access to wide range of allylic amides with a complete transfer of chirality from the allylic imidate starting materials. This was first demonstrated by Shimoda and co-workers, who subjected the *E*-trichloroacetimidate **10** to a thermal Overman rearrangement to give the corresponding trichloroacetamide **12** in a 74% yield with no loss of chirality (Scheme 5).[8] This was a consequence of the reaction progressing *via* a chair-like transition state **11**. This feature can also be observed in the rearrangement of allylic trichloroacetimidates with a *Z*-geometry, such as **24** (Scheme 11).[13]



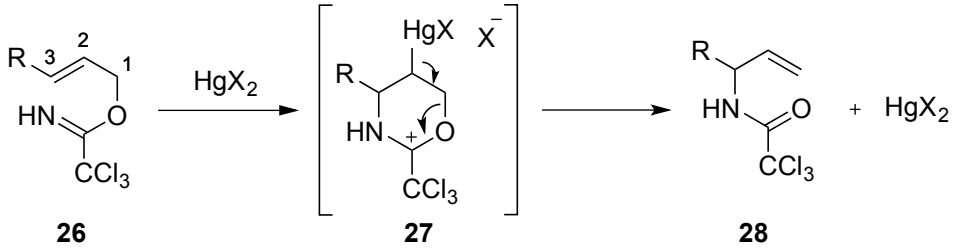
Scheme 11: Chirality transfer in the thermal rearrangement of 24.

1.2.2 Metal catalysed Overman rearrangements

The Overman rearrangement of allylic trihaloacetimidates can be catalysed using various transition metals such as Hg(II), Pd(II), Au(I) or Pt(II).[2b,4,6,14] Therefore, this reaction can be carried out under mild conditions using low temperature, and sometimes resulting in higher yields and cleaner reactions.[6]

1.2.2.1 Mercury (II)-catalysed Overman rearrangement

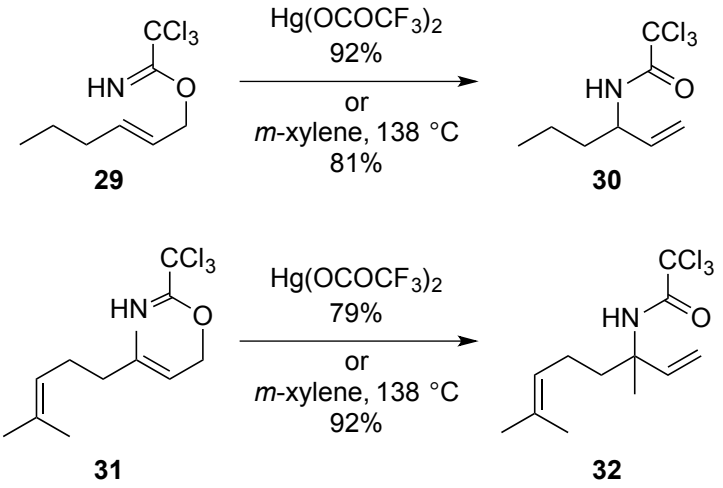
The first catalysed [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates using mercuric salts such as mercuric trifluoroacetate (or mercuric nitrate) was reported by Overman in 1974.[4] It was shown that using mercury(II) as a catalyst increased the reaction rate by up to 10^{12}, allowing the reaction to proceed at room temperature. Therefore, allylic trichloroacetimidate **26** was rearranged to the corresponding allylic trichloroacetamide **28** using Hg(II) as a catalyst under mild conditions (Scheme 12). This transformation involves a two step mechanism in which Hg(II) coordinates to the alkene first, allowing the mercurinium ion to be formed, which then forms intermediate **27** by generation of a Hg–C sigma bond. Secondly, cleaving the C–O bond of the intermediate leads to the formation of the amide product **28**.[4]



26 **27** **28**

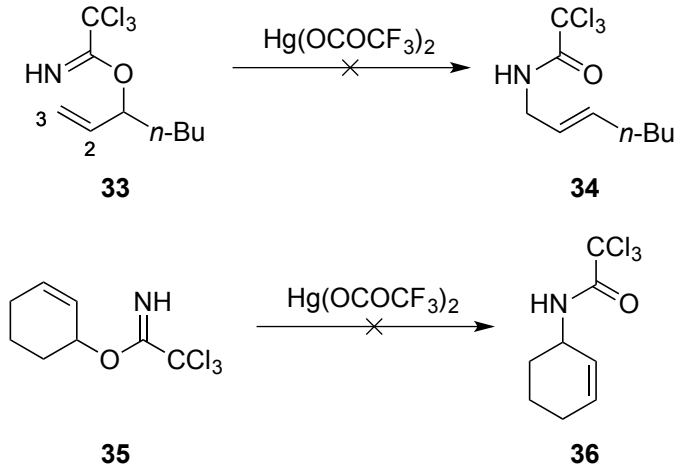
Scheme 12: Mechanism of Hg(II)-catalysed Overman rearrangement.

It has been demonstrated that the catalysed reaction is dependent on the allylic trichloroacetimidate structure, in which the presence of an R group attached to the imidate can promote nucleophilic attack of the imino nitrogen to the C-3 carbon atom.[6] For example, C3-substituted allylic trichloroacetimidates **29** and **31** rearranged successfully to allylic trichloroacetamides **30** and **32** in higher yields at low temperatures, compared to the harsh conditions used for the thermal rearrangement (138 °C) of the same substrates (Scheme 13).



Scheme 13: Early reported examples of Hg(II)-catalysed Overman rearrangement.

However, the scope of the mercuric-catalysed process is limited for other allylic substrates bearing terminal vinyl groups such as **33**, in which the intramolecular nucleophilic addition of the imino nitrogen at C-3 fails to rearrange (Scheme 14).[6] Therefore, the formation of allylic trichloroacetamide **34** is disfavoured, as the imino nitrogen will more likely attack at C-2 position. For the same reason, the Hg(II)-catalysed rearrangement of the cyclic allylic imidate **35** was unsuccessful.



Scheme 14: Limitation of Hg(II)-catalysed Overman rearrangement.

1.2.2.2 Palladium (II)-catalysed Overman rearrangement

Palladium (II)-complexes have become the most successful catalysts since the first reported use of mercuric trifluoroacetate for [3,3]-sigmatropic rearrangements, allowing previously difficult transformations to be performed at room temperature

with lower catalyst loading and minimal amounts of by-products.[15] The Pd(II)-catalysed rearrangement is believed to proceed *via* a cyclisation-induced mechanism, which is similar to that previously proposed by Henry for the Pd(II)-catalysed rearrangement of allylic acetates.[16] This mechanism involves a stepwise pathway, in which the palladium coordinates to the allylic double bond of imidate **37** to initially form complex **38** (Figure 1). This coordination activates the alkene and promotes cyclisation *via* nucleophilic attack by the imidate nitrogen to form the cyclic carbocation intermediate **39**. Cleavage of the Pd−C sigma bond completes the final stage to give acetamide product **40** and regenerates the catalyst.[15−18]

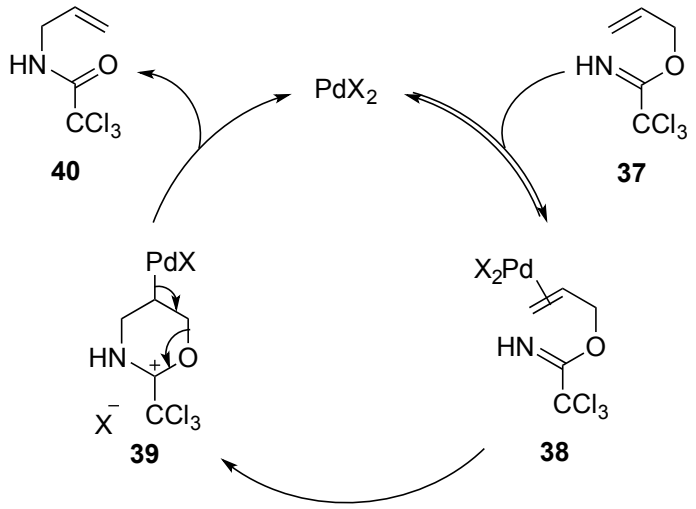
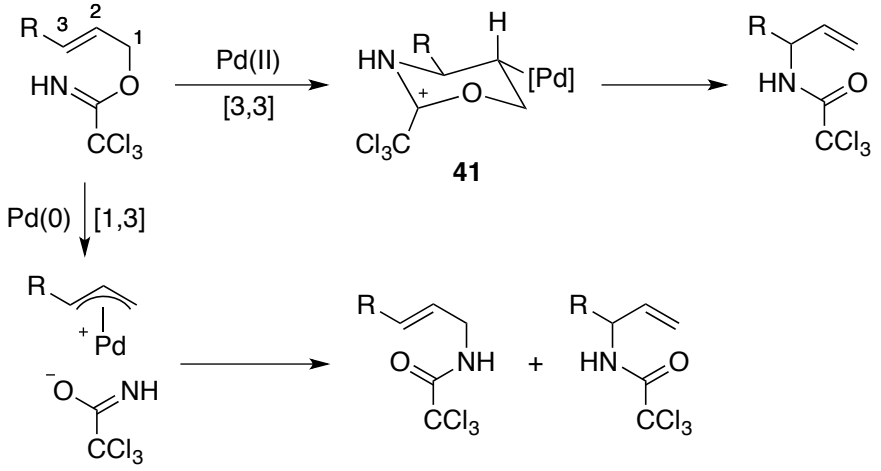


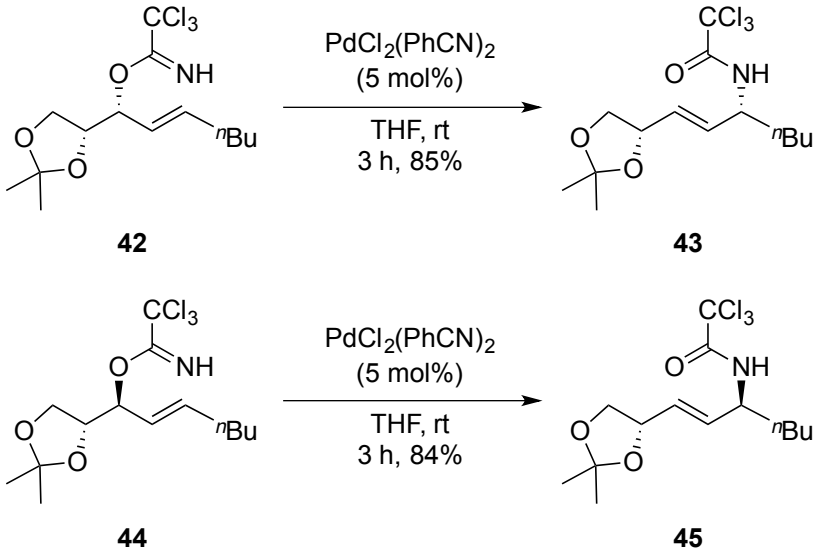
Figure 1: Mechanism of Pd(II)-catalysed Overman rearrangement.

Similar to the thermal reaction, Schenck and Bosnich suggested that the catalytic reaction also proceeds *via* a chair-like transition state (e. g. **41**), in which the palladium catalyst at C2 is placed in the equatorial position, leading to the most stable intermediate.[18] This transition state explains the complete transfer of chirality from the starting imidate to the amide product, as the C−N bond forming takes place on the same face as the cleavage of the C−O bond (Scheme15). The metal catalysis of the Overman rearrangement mainly generates a single [3,3]-sigmatropic product when metal complexes such as $Hg(CF_3CO_2)$, $PdCl_2(CH_3CN)$ and $H_2[PtCl_6]$ are employed. However, the use of zero-valent metal complexes such as $Pd(PPh_3)_4$ and $Pt(PPh_3)_4$ promotes the formation of the [1,3]-rearranged product (*anti*-Claisen) in a competing non-concerted process.[18]



Scheme 15: Mechanisms of [3,3]- and [1,3]-rearrangements.

Recently, palladium (II)-complexes, $PdCl_2(PhCN)_2$ and $PdCl_2(CH_3CN)_2$ have become the most widely used catalysts, which were successfully employed in the rearrangement of wide range of allylic imidates. In 1992, Metz and co-workers reported the Pd(II)-catalysed Overman rearrangement of different secondary allylic trichloroacetimidates.[19] For example, in the presence of $PdCl_2(PhCN)_2$, allylic trichloroacetimidates **42** and **44** rearranged to the desired amide products **43** and **45** in high yields with complete transfer of chirality (Scheme 16).

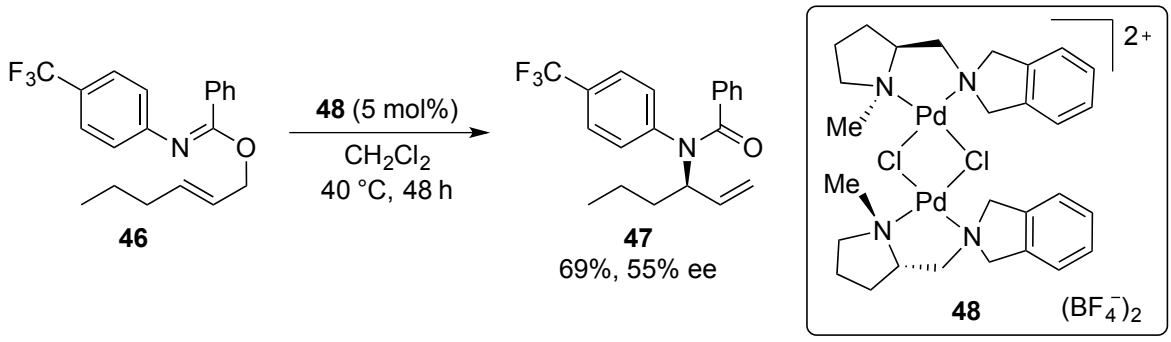


Scheme 16: Pd(II)-Catalysed Overman rearrangement of secondary allylic trichloroacetimidates.

1.2.3 Asymmetric Overman Rearrangement

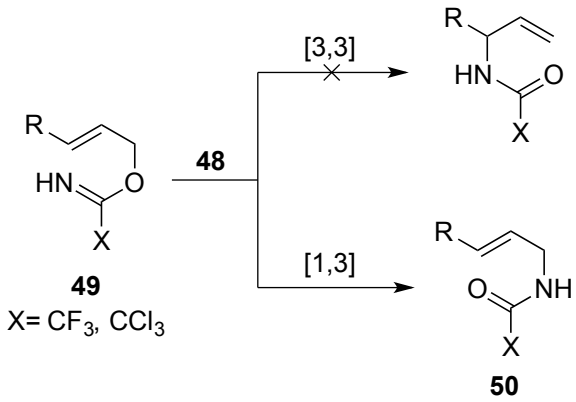
After the success of the metal-catalysed trichloroacetimidate rearrangements, significant attention turned to the development of chiral palladium (II)-catalysts to produce an asymmetric Overman rearrangement. This could then be utilised in the synthesis of important enantiopure nitrogen-containing compounds. During the asymmetric rearrangement process, the catalyst coordinates to one face of the alkene allowing the intramolecular nucleophilic attack by the imino nitrogen to occur at the other unhindered face.[20,21] This then leads to the formation of a single stereoisomer of the desired allylic acetamide.

In 1997, Overman and co-workers reported the first successful application of Pd(II)-complexes for the asymmetric rearrangement of different prochiral allylic imidates.[20] The cationic palladium diamine complex **48** was easily synthesised in four-steps from (*S*)-proline. This catalyst was utilised as an enantioselective catalyst for the rearrangement of various *N*-arylbenzimidates, including **46** to amides such as **47**, in good yield and modest enantiomeric excess (Scheme 17). Hayashi and co-workers then reported a series of cationic oxazoline palladium catalysts for the rearrangement of **46**, and this gave **47** in moderate yields and enantioselectivities (41% yield, 76% ee).[22]



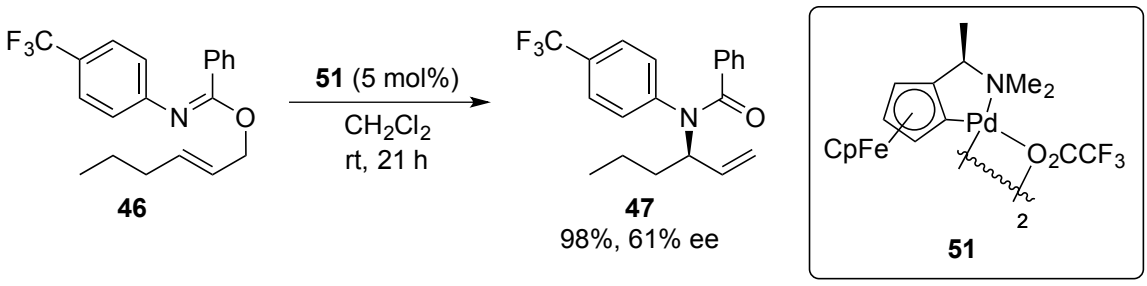
Scheme 17: The first diamine catalyst for enantioselective Overman rearrangement.

However, catalyst **48** failed to rearrange other substrates, e.g. **49** when X= CCl_3 or CF_3, in the same way, and resulted in the formation of the [1,3]-rearranged side-product **50**, as well as other elimination products (Scheme 18).[20]



Scheme 18: [1,3]- and [3,3]-rearrangements pathways.

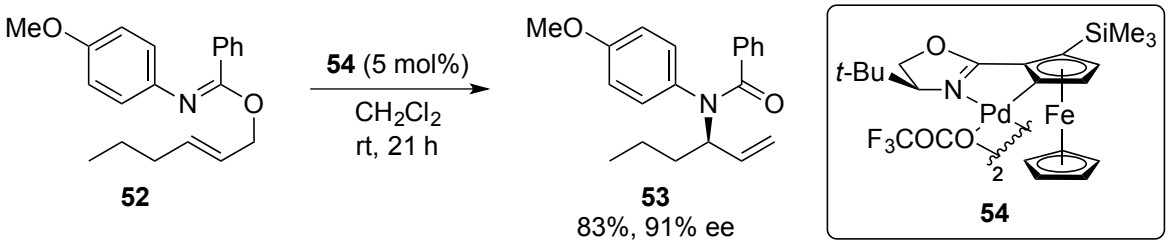
One of the main issues with the cationic complexes was the competing elimination reaction that occurs due to the coordination between the imidate nitrogen and the cationic Pd. To overcome this issue, Overman and co-workers reported the first neutral chiral catalyst, ferrocenyl palladacycle **51**.[23] This catalyst proved to be more effective for the [3,3]-sigmatropic rearrangement of the same benzimidate substrate **46** to benzamide **47**, in greater yield (98%), without the formation of any side-products. However, the enantioselectivity remained moderate (61% ee) (Scheme 19).



Scheme 19: The first reported neutral chiral catalyst, ferrocenyl palladacycle 51.

In an attempt to enhance the enantioselectivity, Donde and Overman developed various ferrocenyl oxazoline palladacycles (FOP) catalysts, including **54**, for the rearrangement of several *E*- and *Z*-allylic *N*-arylbenzimidates, such as **52**.[24] Among all the catalysts, only **54** was found to effectively catalyse the rearrangement and gave benzamide product **53** in excellent yield and greatly improved enantiomeric excess (96% ee) (Scheme 20). However, the scope of the rearrangement using these catalysts was limited to benzimidate substrates only. Thus, this transformation is not useful for the preparation of the corresponding

allylic amines as the 4-methoxyphenyl and benzoyl groups are difficult to remove from the resulting *N*-arylbenzamides.



Scheme 20: Asymmetric Overman rearrangement using FOP catalyst 54.

Other ferrocenyl catalysts, such as **55** (Figure 2) were synthesised by Kang and co-workers and applied to the rearrangement of various allylic benzimidate substrates with *E*- and *Z*-geometry, such as **52**, giving the desired amides in excellent yields and enantioselectivities (**53**, 91% yield and 92% ee) in a shorter reaction time of 0.5 hours.[25] Again, this catalyst was only applicable for benzimidate substrates, which limited the scope of the rearrangement process.

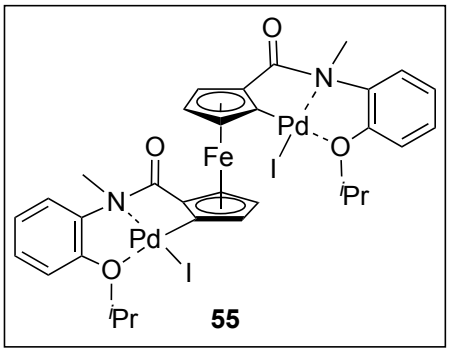


Figure 2: Neutral ferrocenyl catalyst 55.

More recently, the cobalt oxazoline palladacycles (COP-Cl **56** and **57**, Figure 3) have emerged as the most useful asymmetric catalysts to date. Kang and co-workers reported the first use of silver-activated COP-complex (generated *in situ* from the reaction of COP complex **56** and 2 equivalents of silver trifluoroacetate) for the rearrangement of allylic *Z*-benzimidates **58** (Scheme 21).[26] This gave the corresponding rearranged amides **59** in excellent yields and enantioselectivities. On the other hand, moderate yields and enantioselectivities were obtained for the rearrangement of the corresponding allylic *E*-imidates, with the reactions proceeding more slowly.

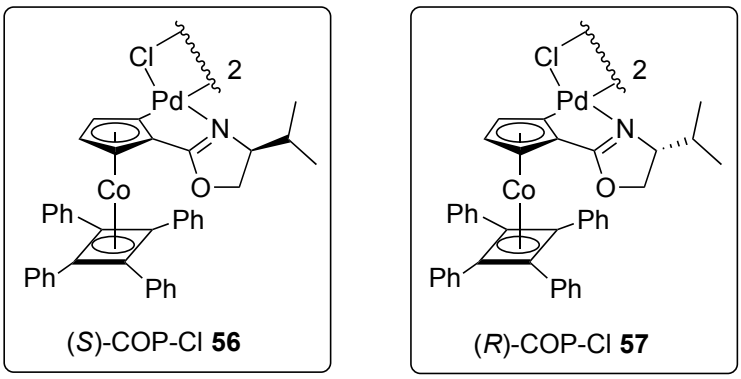
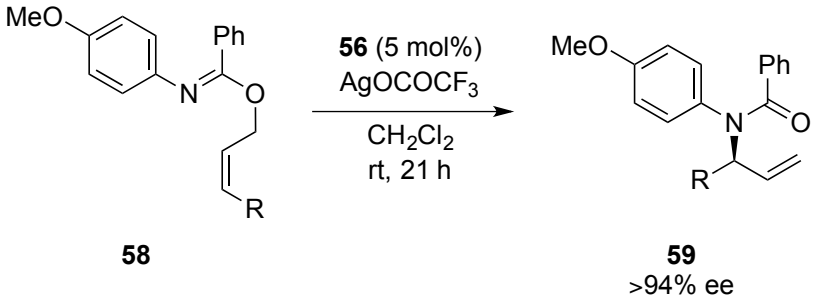
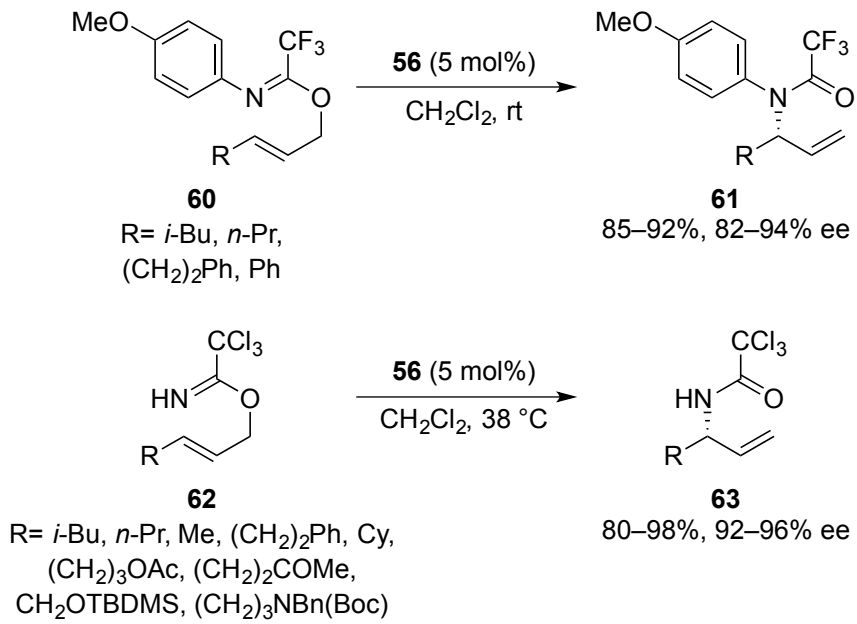


Figure 3: (*S*)- and (*R*)-COP-Cl catalysts.



Scheme 21: Asymmetric rearrangement of allylic *Z*-benzimidates using silver-activated COP Catalyst.

At the same time, Overman and Richards reported the use of COP-Cl complex **56** in the enantioselective rearrangement of *E*-trifluororoacetimidates **60**, giving the rearranged (*S*)-trifluororoacetamide products **61** in excellent yields and high enantioselectivities (Scheme 22).[21] Interestingly, it was found that the COP-Cl catalysts could achieve optimal results for the rearrangement process without pre-activation with silver salts. Moreover, these catalysts also proved to be highly efficient towards other substrates such as *E*-allylic trichloroacetimidates **62**, providing excellent results for the allylic trichloroacetamide products **63**.[27] The allylic trichloroacetimidates are preferred substrates because they can be easily prepared from readily available allylic alcohols in high yields. Also, the trichloroacetyl-protecting group can be removed under basic conditions to form the corresponding chiral allylic amines. However, the COP-catalysed process was not successful with the *Z*-configured imidates, and also when the olefin substituents are bulky (such as *tert*-butyl group) or aryl derived.[27]



Scheme 22: Enantioselective (*S*)-COP-Cl catalysed Overman rearrangement.

More recently, Peters and co-workers reported the synthesis of novel chiral ferrocenyl-imidazoline palladacycle complexes **64a−c** and bispalladacycle catalyst **65** (Figure 4).[28,29] These palladacycles were found to be excellent chiral catalysts for the rearrangement of *Z*- and *E*-configured imidates. Also, they could be a suitable alternative to the COP-Cl complexes, in terms of their efficiency in the rearrangement of *Z*-imidate substrates.

These catalysts were successfully applied to the enantioselective rearrangement of various *Z*- and *E*-configured *N*-*para*-methoxyphenyl-trifluoroacetimidates **60**, affording the corresponding allylic trifluoroacetamides **61** in excellent yields and enantioselectivities (Table 1). Complex **64c** was found to be most effective for the rearrangement of allylic *E*-imidates.[28] With the *Z*-configured substrates; excellent results were obtained using palladacycles **64a** and **64b** or bispalladacycle **65**.[28,29] In contrast to other catalysts, it is possible to lower the catalyst loading to 0.05 mol%, without affecting the reaction outcome. However, these catalysts still require pre-activation with silver salts.

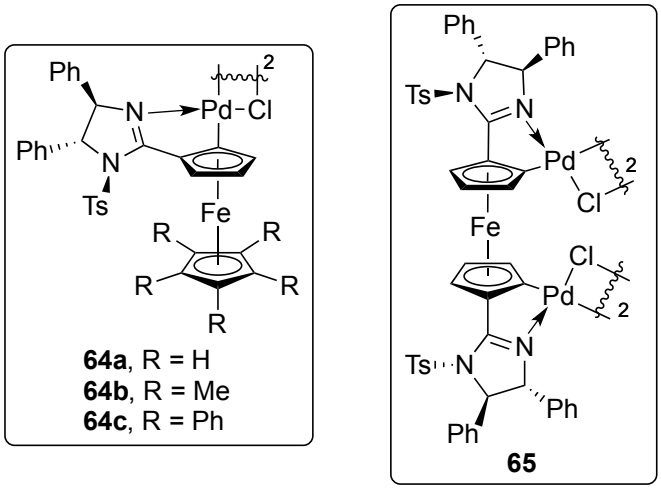
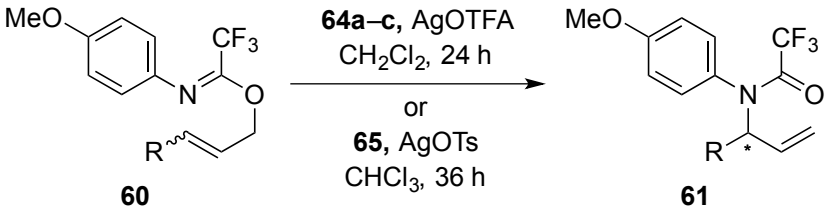


Figure 4: Chiral ferrocenyl-imidazoline palladacycle 64a−c and bispalladacycle 65.



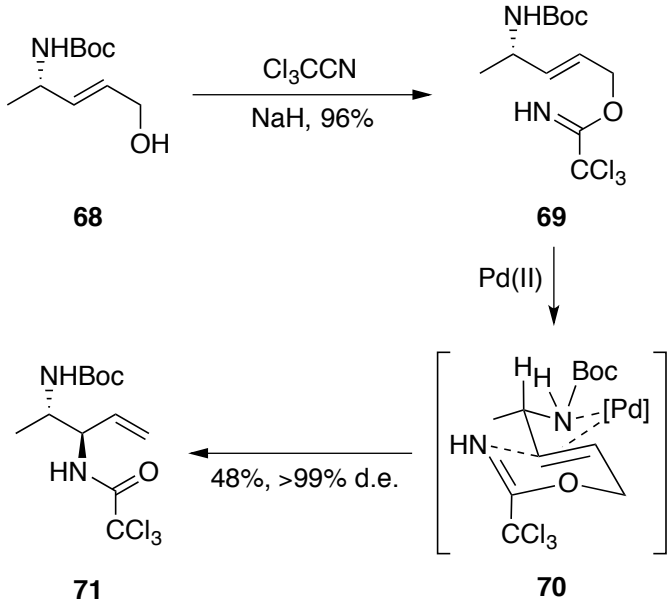
Entry	R	Geometry	Catalyst (mol %)	Temp. (°C)	Yield (%)	ee (%)
1	*n*-Pr	*Z*	**64a**, 5	20	75	89 (*S*)
2	$(CH_2)_2Ph$	*Z*	**64a**, 5	20	70	90 (*S*)
3	*i*-Bu	*Z*	**64a**, 5	20	69	96 (*S*)
4	*n*-Pr	*Z*	**64b**, 5	40	72	93 (*S*)
5	$(CH_2)_2Ph$	*Z*	**64b**, 5	40	95	95 (*S*)
6	*i*-Bu	*Z*	**64b**, 5	40	82	96 (*S*)
7	*n*-Pr	*E*	**64c**, 0.05	40	95	95 (*R*)
8	*n*-Pr	*Z*	**64c**, 5.0	40	36	85 (*S*)
9	Me	*E*	**64c**, 0.05	40	98	92 (*R*)
10	$(CH_2)_2Ph$	*E*	**64c**, 0.05	40	99	98 (*R*)
11	*i*-Bu	*E*	**64c**, 0.2	40	96	98 (*R*)
12	*n*-Pr	*Z*	**65**, 1.0	20	96	98 (*S*)
13	Me	*Z*	**65**, 1.0	20	94	96 (*S*)
14	$(CH_2)_2Ph$	*Z*	**65**, 1.0	20	99	96 (*S*)
15	*i*-Bu	*Z*	**65**, 1.0	20	87	98 (*S*)

Table 1: Enantioselective rearrangement results with palladacycle catalysts 64a−c and 65.

1.2.4 Substrate directed palladium(II)-catalysed Overman rearrangement

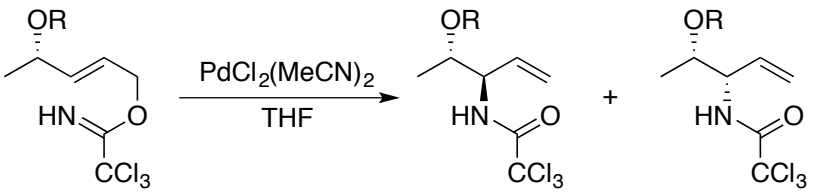
A substrate-directed Overman rearrangement is an important approach that can be used to introduce stereoselectivity without employing a chiral catalyst. This involves the use of an imidate substrate bearing a chiral directing group adjacent to the alkene. This chiral functionality can be used to direct the catalyst to one face of the alkene, allowing nucleophilic attack by the imidate nitrogen to take place at the least hindered face of the substrate. This then leads to stereochemical control during the rearrangement process.

In 1993, Belluš and co-workers reported the first example of a substrate directed Overman rearrangement for the synthesis of 1,2-diamines.[30] In this example, allylic trichloroacetimidate **69** was first prepared in 96% yield from allylic alcohol **68** (containing chiral a Boc-protected amine in the vicinity of the alkene) (Scheme 23). This amine-directing group was successfully utilised in the Pd-catalysed rearrangement of **69** to give the *anti*-diastereomer **71** as a major product in excellent diastereoselectivity and modest yield. The high diastereoselectivity was explained using a chair-like transition state **70**, with the palladium coordinating to the amine nitrogen and the alkene.



Scheme 23. The first example of a substrate directed Overman rearrangement.

The substrate directed process was further investigated within the Sutherland research group using different ether chiral directing groups. Work by Jamieson and Sutherland showed that unhindered ether directing groups could be effectively used to direct the palladium catalyst in a similar way to that described above by Bellûs.[31] In this study, a number of allylic trichloroacetimidates **72** having different ether groups were synthesised and then subjected to Pd-catalysed Overman rearrangement (Table 2). The methoxymethyl (MOM) group was found to be the most effective directing group to give the *anti*-diastereomer **73a** as a major product in 10:1 ratio with 64% yield (entry 5). The higher observed diastereoselectivity was attributed to the catalyst coordinating to both oxygen atoms of the MOM group. On the other hand, bulky ether groups prevented coordination of the metal catalyst to the alkene and gave products in poor selectivities (entries 1, 2, 3).



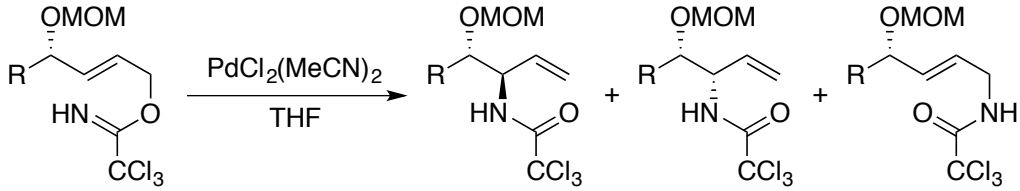
72 **73a** **73b**

Entry	R	Yield (%)	Ratio (**73a**:**73b**)
1	TBDMS	68	2:1
2	Tr	70	3:1
3	Bn	62	3:1
4	Me	49	7:1
5	MOM	64	10:1
6	MEM	60	8:1

Table 2: Substrate directed rearrangement of allylic trichloroacetimidate 72 containing different ethers.

Using the MOM-ether as a directing group, Sutherland and co-workers further expanded the scope of this process.[32] Several allylic trichloroacetimidates **74** with a variety of side chains were synthesised and subjected to the substrate directed rearrangement process. This allowed the formation of the desired *anti*-

diastereomers **75a** in good yield with excellent diastereoselectivity (Table 3, entries 1, 2 and 3). It was noticed that trace amounts of the [1,3]-rearranged product **57c** was formed. As previously demonstrated by Ikariya and Bosnich, this by-product is normally observed when palladium(0) catalyst exists in the reaction mixture.[17,18] The Pd(0) was believed to be formed due to the slower rearrangement of the bulkier substrates, *via* a competing β-elimination process. This issue was overcome by the addition of *p*-benzoquinone, a re-oxidant used to convert Pd(0) to Pd(II). This effectively suppressed the formation of [1,3]-products and led to the desired [3,3]-products more cleanly (entries 4, 5 and 6). Further oxidation and deprotection of the resulting allylic trichloroacetamides **75a** led to the corresponding β-hydroxy-α-amino acids. More recently, the Sutherland group also examined the ether-directed Overman rearrangement process using a variety of metal catalysts and solvents. The best results were achieved using Pd(II) or Pt(II) catalysts in THF or toluene.[33]



74 **75a** **75b** **75c**

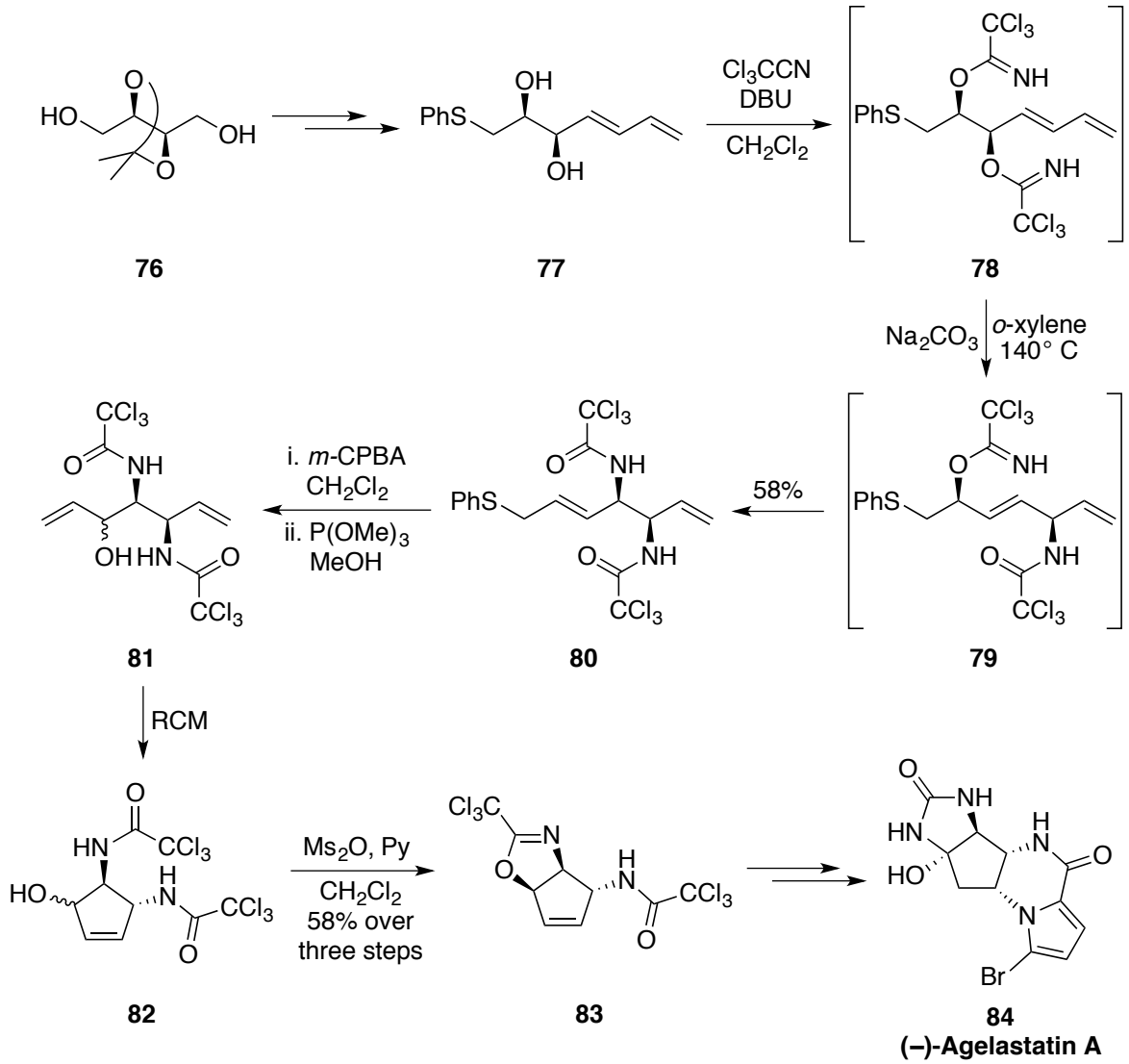
Entry	R	Additive	Yield (%)[a]	Ratio (**75a**:**75b**:**75c**)
1	*i*-Bu	-	60	14:1:1
2	$PhCH_2$	-	54	12:1:0
3	$PhCH_2CH_2$	-	65	9:1:4
4	*i*-Bu	*p*-benzoquinone	73	14:1:0
5	$PhCH_2$	*p*-benzoquinone	70	12:1:0
6	$PhCH_2CH_2$	*p*-benzoquinone	69	9:1:0

Table 3: Scope of MOM-ether directed Overman rearrangement. [a]Isolated combined yields of 75a, 75b and 75c from allylic alcohol.

1.2.5 Applications of the Overman rearrangement

The Overman rearrangement has found widespread application in synthetic organic chemistry.[34] As previously mentioned, this is due to the relative ease of preparation of the allylic trichloroacetimidates from readily available allylic alcohols as well as the high yields obtained for the final allylic amide products. The Overman rearrangement is especially important because of its ability to generate new stereocentres. Also it can provide products in high stereoselectivity, due to the complete transfer of chirality from allylic alcohols to the new C−N bond. Moreover, removal of the trichloroacetyl-protecting group to form allylic amines has then allowed access to wide variety of nitrogen-containing products including natural products, amino acids, amino sugars, peptides, modified nucleotides and other *N*-heterocycles.[5,34]

For example, (–)-agelastatin A (**84**), a marine alkaloid was isolated from axinellid sponge *Agelas dendromorpha*.[35] It is identified as an antimetastatic and antineoplastic agent and also shows insecticidal properties.[36−38] In 2009, Chida and co-workers reported the use of a cascade thermal Overman rearrangement as a key transformation for the synthesis of this target (Scheme 24).[39] In this synthesis, allylic diol **77** was first prepared in multiple steps from a commercially available (–)-2,3-*O*-isopropylidene-D-threitol (**76**). In the presence of trichloroacetonitrile and base, allylic vicinal diol **77** was converted to the corresponding allylic bistrichloroacetimidate **78,** which then underwent a sequential thermal Overman rearrangement to produce the bistrichloroacetamide **80** in 58% overall yield. The observed transfer of chirality from allylic alcohol **77** to the new C−N bond was a direct consequence of the concerted nature of the Overman rearrangement. A Mislow-Evans rearrangement was then employed to produce the hydroxyl group at the C5 carbon. Subsequent ring closing metathesis of **81** gave cyclopentene **82**, which upon treatment with methanesulfonic anhydride afforded the oxazoline **83** in 58% yield over three steps. Further functionalisation of oxazoline **83** to install the piperazinone ring completed the synthesis of (–)-agelastatin A (**84**).

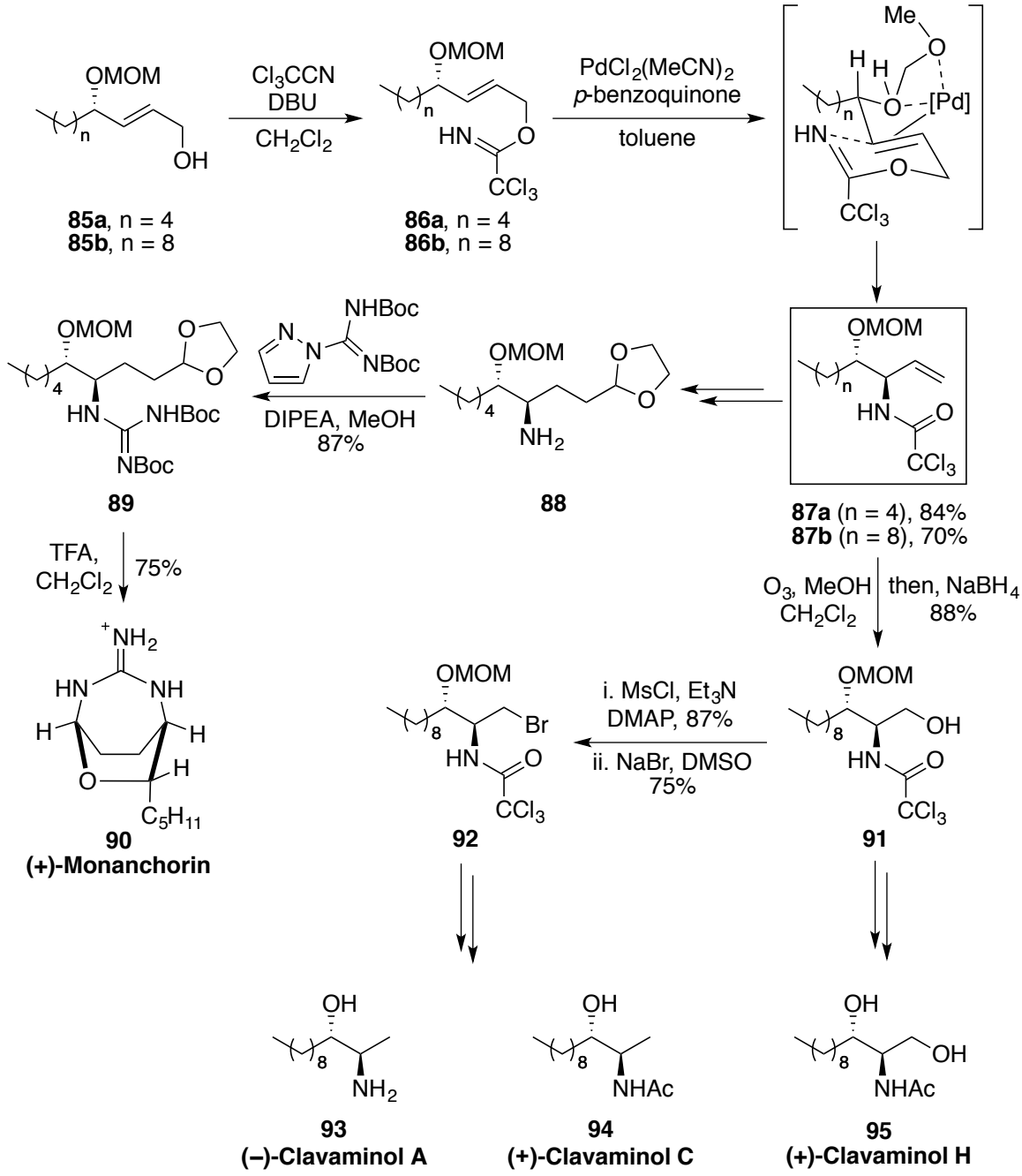


Scheme 24: The total synthesis of (–)-agelastatin A (84) using a cascade thermal Overman rearrangement.

Within the Sutherland research group, the palladium(II)-catalysed MOM-ether directed Overman rearrangement has been employed for the stereoselective synthesis of several biologically active molecules and natural products.[32,40–43] For example, (+)-monanchorin (**90**), a guanidine alkaloid isolated from the sponge *Monanchora ungiculata*.[44] The Pd(II)-catalysed Overman rearrangement was used as a key step to generate the second stereogenic centre. Initially, the desired allylic alcohol **85a** was prepared and then treated with trichloroacetonitrile and DBU to obtain allylic trichloroacetimidate precursor **86a** (Scheme 25).[41] The imidate **86a** was then subjected to the Pd-catalysed MOM-ether directed Overman rearrangement. This gave the corresponding trichloroacetamide **87a** in 84% yield

with a 12:1 diastereomeric ratio between the *anti* and *syn* [3,3]-products. *p*-Benzoquinone was added to the reaction mixture to inhibit the formation of the [1,3]-by-product, resulting in an improved yield of the major anti-diastereomer. The amine of the major diastereomer **87a** was then re-protected as benzyloxy carbamate. This was followed by a cross metathesis with 2-vinyl-1,3-dioxolane and then hydrogenation to form the amine **88**. Coupling of amine **88** with a commercially available guanylation reagent gave **89** in 87% yield. Finally, treatment of **89** with TFA completed the synthesis of the natural product (+)-monanchorin (**90**).

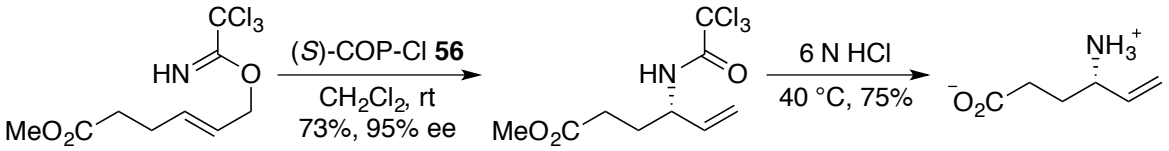
More recently, the Sutherland group utilised the same methodology for the synthesis of clavaminols A (**93**), C (**94**) and H (**95**) (Scheme 25).[42] Clavaminols are a class of amino alcohols isolated from the Mediterranean ascidian *Clavelina phlegraea*.[45,46] These compounds, in particular (–)-clavaminol A, have shown cytotoxic properties against a number of cancer cell types such as breast, lung and gastric.[46] In this synthesis, the Pd(II)-catalysed Overman rearrangement of allylic trichloroacetimidate **86b** gave the *anti*-product **87b** as a major diastereomer in 13:1 ratio. The *anti*-diastereomer **87b** was isolated in 70% yield. Under reductive conditions, ozonolysis of the allylic trichloroacetamide **87b** gave alcohol **91** in 88% yield. Reduction of the trichloroacetyl group of **91** using *n*-tributyltin hydride followed by selective deprotection of the MOM group gave the desired (+)-clavaminol H (**95**). To form the methyl side-chain, alcohol **91** was converted to the corresponding bromide **92**. Cleavage of the C−Br bond and reduction of the trichloroacetyl group in a one-pot reaction, followed by selective deprotection of the MOM group gave (+)-clavaminol C (**94**). Removal of both protecting groups gave (–)-clavaminol A (**93**).



Scheme 25: Pd(II)-Catalysed MOM-ether directed Overman rearrangement for the stereoselective synthesis natural products 90, 93, 94 and 95.

In 2003, Overman and co-workers reported the successful use of a chiral palladium catalyst [(*S*)-COP-Cl **56**] for the enantioselective synthesis of various allylic trichloroacetimidates to the corresponding allylic trichloroacetamides (Scheme 22).[27] In the same paper, they applied this methodology for the synthesis of the natural product (*S*)-vigabatrin (**96**) (Scheme 26). Initially, asymmetric Pd(II)-catalysed Overman rearrangement of **62** using (*S*)-COP-Cl **56** gave allylic

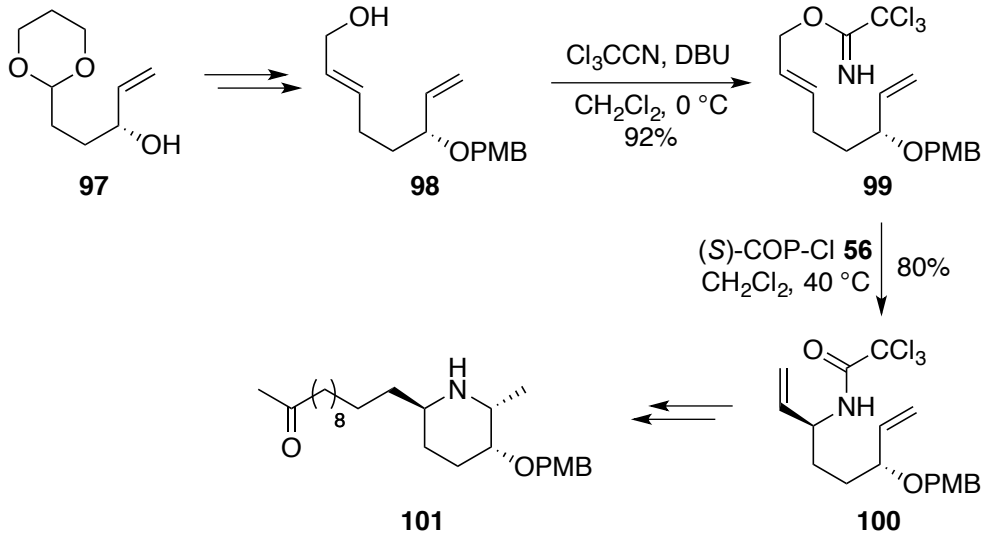
trichloroacetamide **63** in 73% yield and 95% ee which was then after treatment with 6 N HCl gave (*S*)-vigabatrin (**96**) in 75% yield.



62 **63** **96**
(*S*)-Vigabatrin

Scheme 26: Asymmetric synthesis of (*S*)-vigabatrin using (*S*)-COP-Cl.

Since then there have been only a few examples appeared in the literature for using COP catalysts in natural products synthesis. One of these was reported by Han and co-workers for their synthesis of the trisubstituted piperidine (+)-*iso*-6-cassine (**101**), which is an important core structure of several biologically active compounds (Scheme 27).[47] An asymmetric Overman rearrangement of **99** using (*S*)-COP-Cl **56** was carried out to form allylic trichloroacetamide **100**. The Overman rearrangement was essential to generate the second stereocentre of the target compound. An intramolecular amidomercuration reaction to establish the third stereocentre followed by cross metathesis to attach the side-chain then gave compound **101**.



97 **98** **99**
100
101
(+)-*iso*-6-Cassine

Scheme 27: Synthesis of (+)-*iso*-6-cassine using a (*S*)-COP-Cl catalysed Overman rearrangement.

1.2.6 Conclusions

The Overman rearrangement has been used as a key step in the synthesis of a wide range of nitrogen-containing products including natural products, amino acids and other *N*-heterocycles. This reaction can provide products in high yields and stereoselectivity and it is especially important because of its ability to generate new stereocentres. Recently, advances have been made toward the synthesis of chiral palladium catalysts such as the COP-Cl catalysts. These catalysts have been successfully employed in natural products synthesis. In addition, substrate-directed Overman rearrangement has been recently developed as an alternative way to introduce stereoselectivity without employing a chiral catalyst. This approach has been successfully employed in the synthesis of a variety of amino acids, amino alcohols and alkaloid natural products.

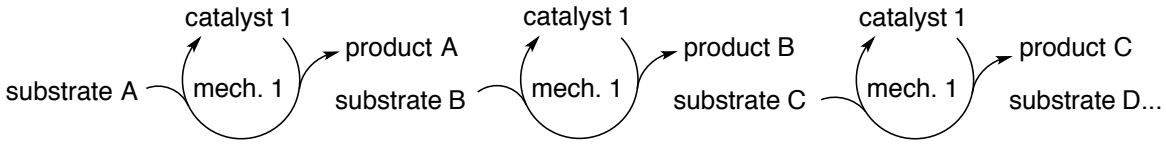
1.3 One-pot multi-step processes

Enhancing the efficiency and handling of waste are two major issues in modern organic chemistry. These concepts should be considered carefully during the design of any synthetic process.[48] In other words, these can be described in terms of reducing the number of synthetic steps to a target compound (step economy),[49] incorporating all atoms of each reagent into the final product (atom economy),[50,51] and avoiding isolation and purification of intermediates as necessary by carrying out as many sequential transformations in the same reactor (pot economy).[52] This in turn means reducing the amount of reagents and solvents, leading to significant reduction of waste which would lead to greener synthetic methods. To meet this aim, organic chemists have recently turned attention to the development of one-pot multi-bond forming processes as efficient synthetic methodologies that allows the synthesis of complex structures from simple and readily available starting materials.[48,53,54]

Generally, the term “one-pot process” refers to a process in which multiple transformations and bond-forming steps can take place in a single reaction vessel, without isolation or purification of intermediates.[53,54–57] This makes dealing with unstable, toxic, volatile and sensitive intermediates easier. The use of these processes helps to minimise the amount of solvents and reagents as well as reducing waste, which can lead to great benefits for the environment. Other advantages of developing one-pot processes are reduction of cost and time and also increasing the chemical yield. In general; the one-pot process is an effective way to make the chemical reaction more efficient. One-pot processes can be generally classified into three different terminologies: domino/cascade, tandem or classical one-pot multi-step process.[57]

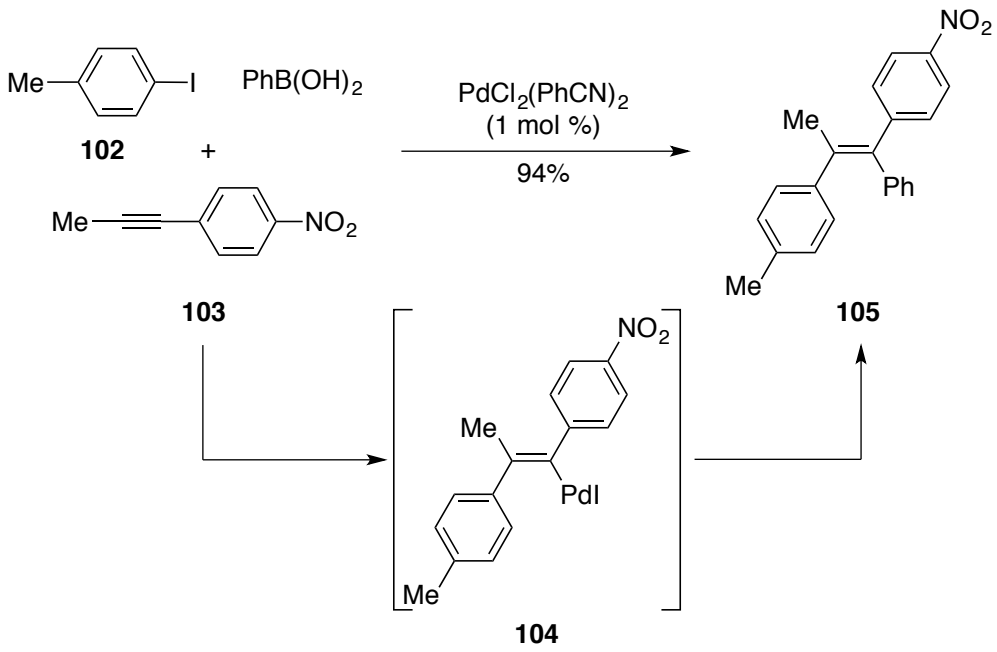
1.3.1 Domino/cascade catalysis

The domino reaction, sometimes identified as a cascade reaction, is an important approach in organic chemistry for the synthesis of complex structures. This type of reaction was defined, by Tietze, as “a process involving two or more bond-forming transformations which take place under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step” (Scheme 28).[58] Faber has further added that “both individual reactions belong tightly together and are rather difficult to perform in a stepwise fashion. As a consequence, the intermediate between both steps is likely to be unstable and eludes isolation and characterisation”.[59] Fogg additionally stated that all transformations are involved in a single reaction mechanism.[57] The cascade type catalysis was defined by Fogg as multiple (≥3) domino reactions.[57]



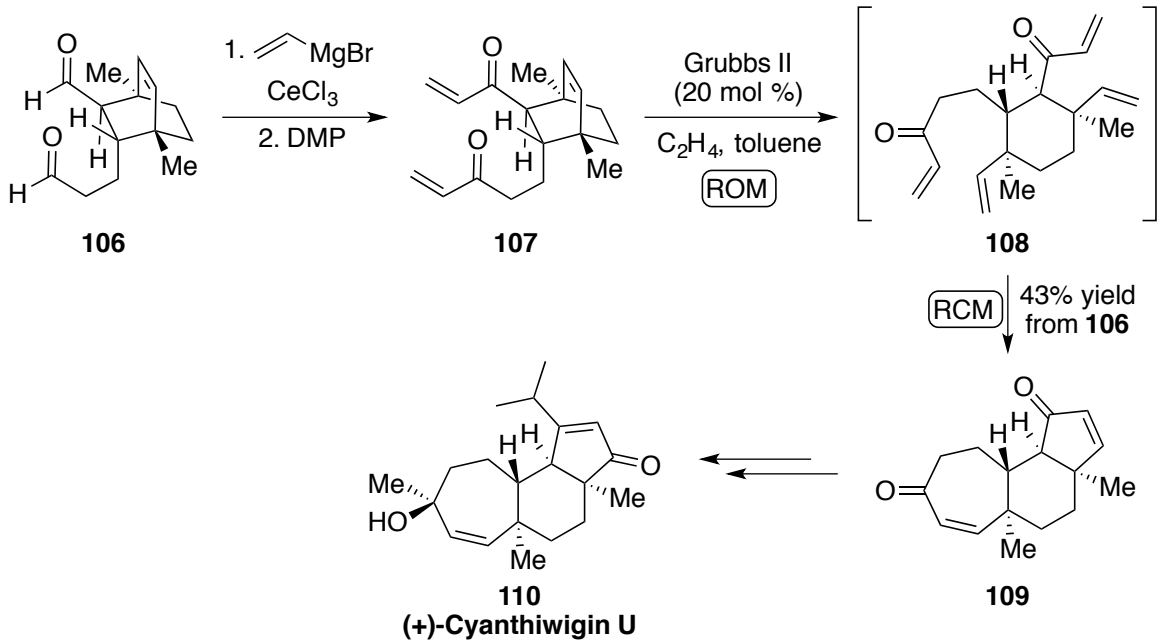
Scheme 28: Illustration of domino/cascade process.

Palladium catalysed transformations are of great importance for the construction of carbon−carbon bond and have been widely utilised in domino and cascade catalysis. In 2003, Larock and co-workers reported a typical example of a domino reaction for the synthesis of tetrasubstituted alkene **105** (Scheme 29).[60] The first step of this transformation is a regioselective carbopalladation of **103** with an aryl palladium intermediate generated from the oxidative addition of aryl halide **102** with Pd(0), to form the vinylic palladium intermediate **104**. Subsequent Suzuki-type transmetalation followed by reductive elimination gave tetrasubstituted alkene product **105** in 94% yield.



Scheme 29: Palladium catalysed synthesis of tetrasubstituted alkene 105.

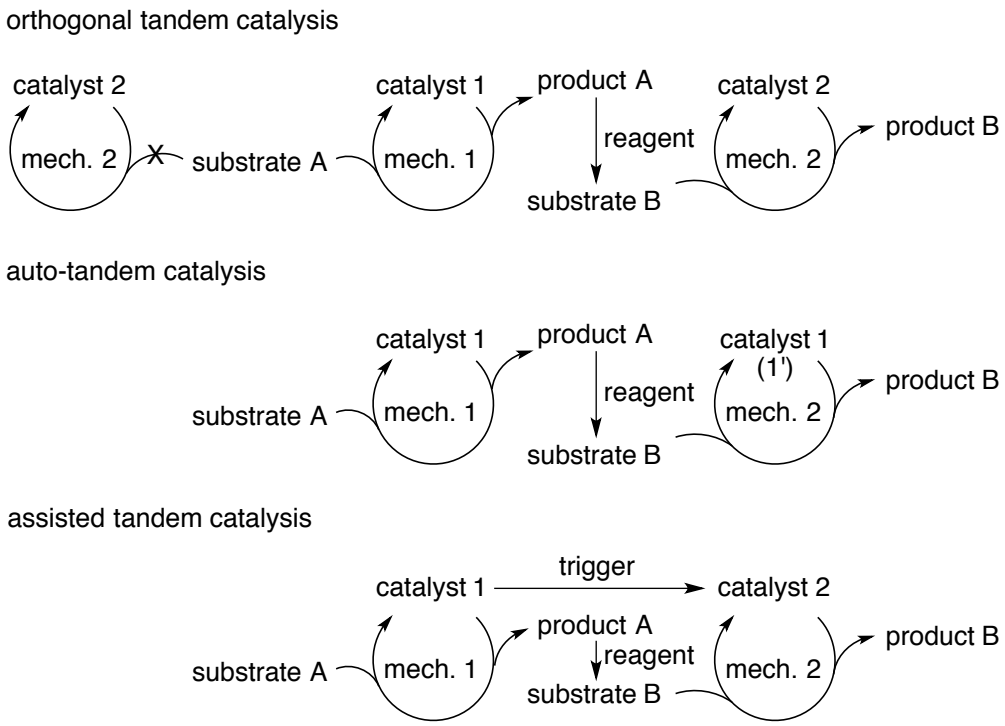
An example of cascade reactions using ruthenium complexes was reported by Phillips and Pfeiffer who utilised a two directional metathesis cascade process in their synthesis of the natural product (+)-cyanthiwigin U (**110**) (Scheme 30).[61] Bis-enone **107** was first prepared from dialdehyde **106**, and then treated with Grubbs second-generation catalyst (Grubbs II) to initiate the ring-opening metathesis (ROM) reaction and produce intermediate **108.** This was followed by two sequential ring-closing metathesis (RCM) reactions to give tricyclic core **109** in 43% overall yield from dialdehyde **106**. A five further steps completed the total synthesis of **110**.



Scheme 30: Cascade ROM/RCM process for the synthesis of (+)-cyanthiwigin U (110).

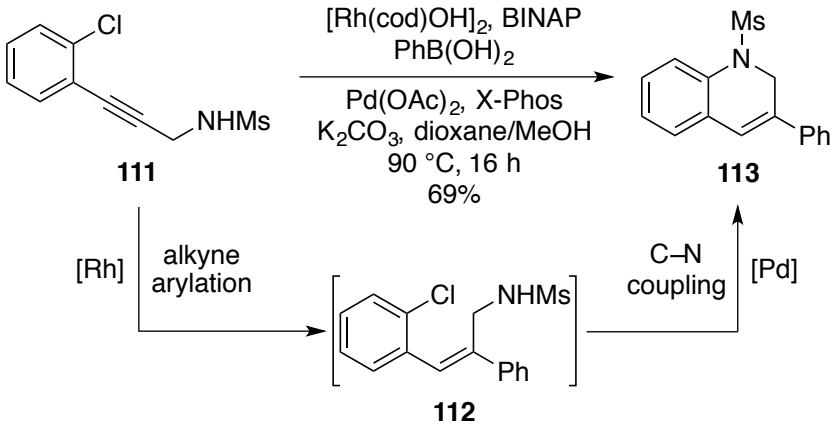
1.3.2 Tandem catalysis

The term tandem catalysis was described as a multiple catalysis process in which sequential reactions of the substrate take place *via* two or more distinct mechanisms (Scheme 31).[56,57] In this process, intermediates are more likely to be stable. According to Fogg's classification, the tandem catalysis was further divided into three different categories: orthogonal, auto- and assisted tandem catalysis.[57] Orthogonal catalysis involves two (or more) distinct and non-interfering catalysts, each of them catalyses an independent transformation and all must be present (with any other required reagents) from the reaction outset.[56,57,62] In the auto-tandem catalysis, only a single catalyst is used to effect two (or more) distinct transformations in two different mechanisms, without adding reagents to prompt any change in mechanism.[56,57,63,64] In a similar way, a single catalyst is still employed in the assisted catalysis, except that after the completion of the first cycle, reagents must be added to trigger a change in the catalyst and start another cycle.[56,57]



Scheme 31: Illustration of tandem catalysis.

One of the most popular uses of the tandem catalysis has been in the synthesis of heterocyclic scaffolds using different metal-ligand combinations. Recently, Lautens and co-workers reported the synthesis of dihydroquinolines **113** *via* a rhodium/palladium-catalysed orthogonal tandem process (Scheme 32).[65] The process started with a Rh-catalysed alkyne arylation of disubstituted alkyne **111** to form the phenylallyl **112**. This was followed by a Pd-catalysed C−N coupling reaction to furnish the desired dihydroquinoline **113**. Control experiments were carried out to investigate the catalyst−ligand compatibility. It was found that Rh/X-Phos and Pd/BINAP display low reactivity for the arylation reaction (5% yield with partial decomposition of starting material **111**) and no reaction for the C−N coupling. Ligand-free arylation only led to decomposition of **111**. The authors also found that palladium can bind equally and competitively to both ligands. To overcome this issue, catalysts were premixed with their specified ligands and then added to the reaction mixture to enable the formation of the final product in high overall yield.



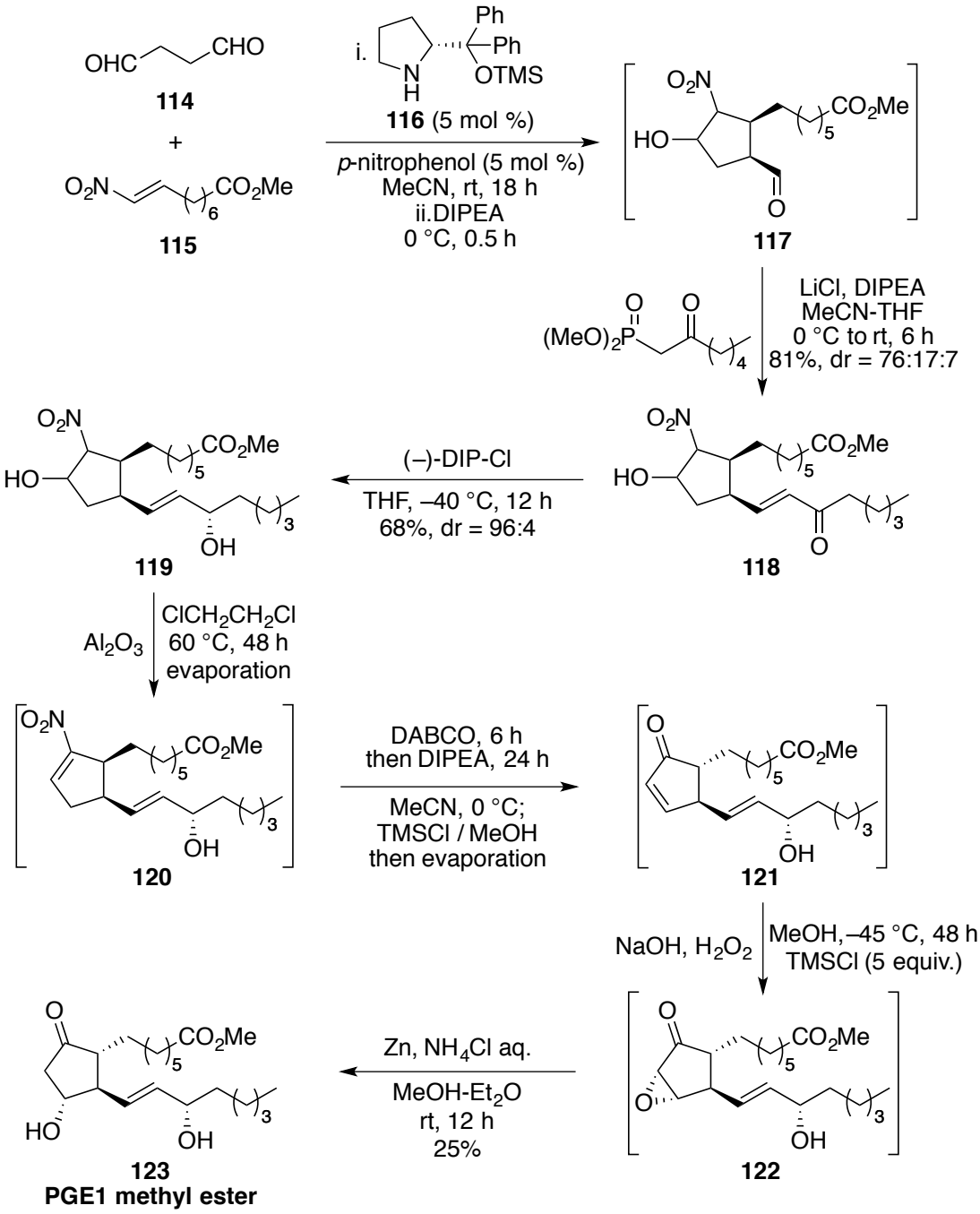
Scheme 32: Rh/Pd-catalysed orthogonal tandem process for the synthesis of dihydroquinoline 113.

1.3.3 Classical one-pot multi-step process

Classical one-pot multi-step process (one-pot synthesis) can simply combine all previous terminologies (domino/cascade and tandem) except that catalysts and reagents can be added any time during the one-pot process as needed, which make these processes easier to develop and can have broader scope.[54,57,66]

The concept “pot economy”, which was proposed by Clarke, is based on carrying out several sequential transformations in the same reactor without isolation or purification of intermediates.[52] This pot economic approach has been effectively demonstrated in the total synthesis of natural products and medicinally important compounds.[67–71] For example, Hayashi and Umemiya employed a three-pot process in their synthesis of prostaglandin E_1 (PGE_1) methyl ester (**123**) (Scheme 33).[71] The first one-pot reaction started with an asymmetric Michel addition of succinaldehyde **114** and nitroalkene **115** using organocatalyst **116**, followed by an intramolecular Henry reaction to obtain the cyclopentane **117**. Subsequent Horner-Wadsworth-Emmons reaction then afforded the prostaglandin skeleton **118** in 81% yield over the four-step process with high diastereoselectivity. As **117** is unstable, it was important to carry out the HWE reaction in the same pot, where in an attempt to isolate **117**, the yield was low. A diastereoselective reduction of ketone **118** in a single pot using (**–**)-diisopinocamphenyl chloroborane (DIPCl) gave allylic alcohol **119** in 68% yield. In a second one-pot process, further functionalisation of the cyclopentyl ring completed the synthesis of PGE_1 methyl ester **123** in 14%

overall yield.

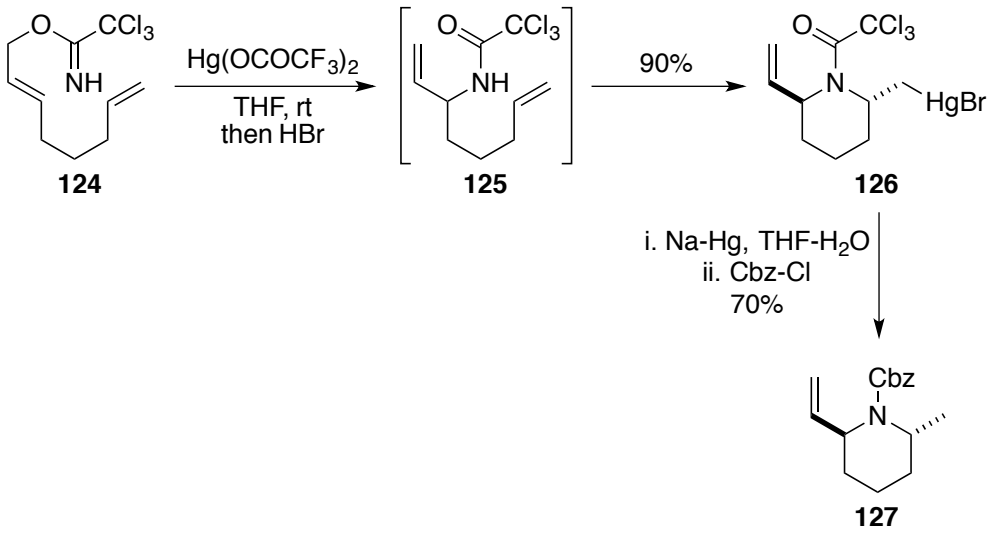


Scheme 33: Three-pot synthesis of PGE_1 methyl ester (123).

1.3.4 One-pot process initiated by Overman rearrangement

The Overman rearrangement is an important tool in C–N bond formation, and has been extensively used as a single step in the total synthesis of natural products, and other valuable compounds.[34] This reaction can be also combined with other

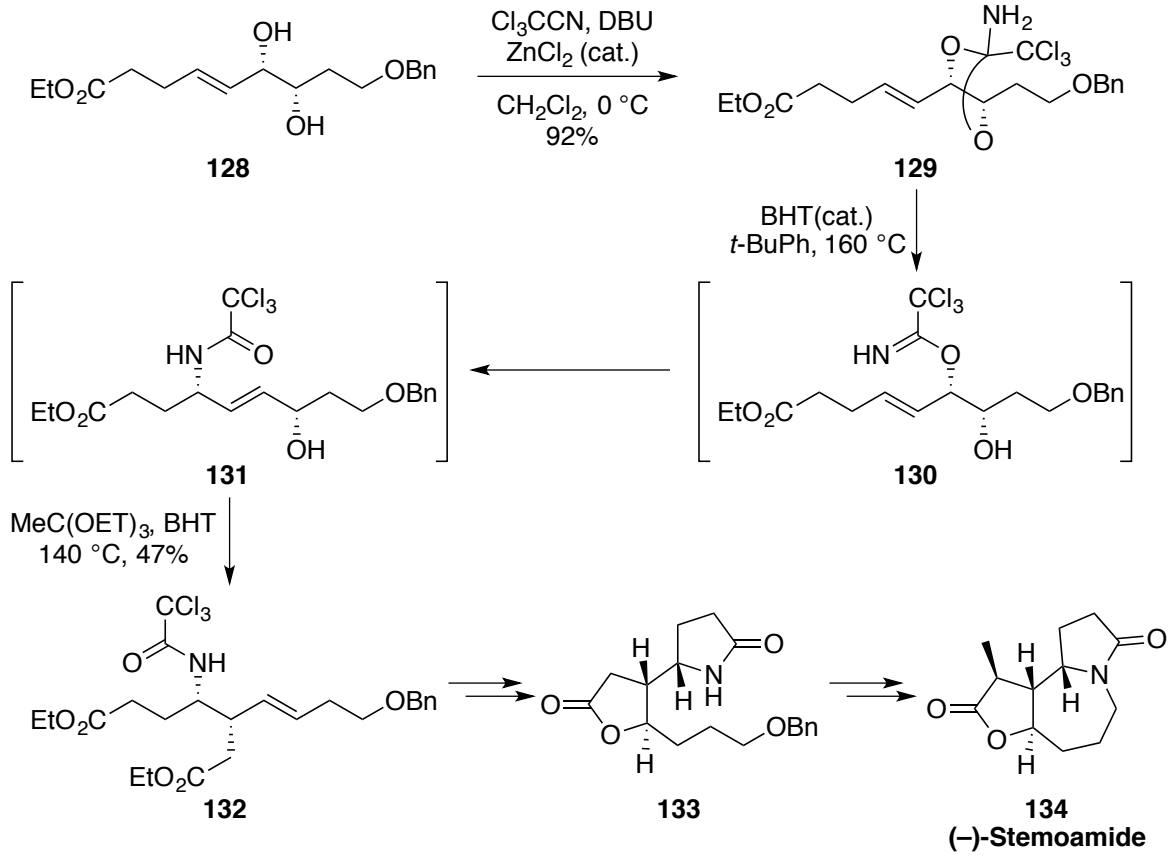
transformations in one-pot processes. For example, a mercury(II)-mediated one-pot tandem Overman rearrangement/intramolecular amidomercuration process was reported by Han and Singh for the synthesis of *trans*-2,6-dialkylpiperidine **127** (Scheme 34).[72] The tandem process was initiated by treatment of allylic trichloroacetimidate **124** with mercury(II) catalyst to form allylic amide **125** which then underwent an intramolecular amidomercuration reaction to produce the desired piperidine product **126** in 90% yield. In another one-pot process, demercuration of **126** followed by reprotection of the amine group gave **127** in 70% yield.



Scheme 34: A mercury(II)-mediated tandem Overman rearrangement/intramolecular amidomercuration reaction for the synthesis of *trans*-2,6-dialkylpiperidine 127.

Another example of one-pot reactions initiated by Overman rearrangement was reported by Chida and co-workers for the synthesis of the natural product (–)-stemoamide (**134**) (Scheme 35).[73] In the presence of DBU and $ZnCl_2$ (catalytic), allylic diol **128** was treated with trichloroacetonitrile to form cyclic orthoamide **129**. The use of $ZnCl_2$ was important to prevent the formation of the undesired bis-trichloroacetimidate. Compound **129** was then heated to initiate the ring opening and generate imidate **130**. In the same pot, compound **130** was subjected to the Overman rearrangement to form allylic amide **131**. Allylic alcohol of **131** then underwent a Johnson-Claisen rearrangement using triethyl orthoacetate and 2-nitrophenol to form the rearranged product **132** as a single diastereomer in 47% overall yield. Furthermore, both esters of **132** were hydrolysed to the

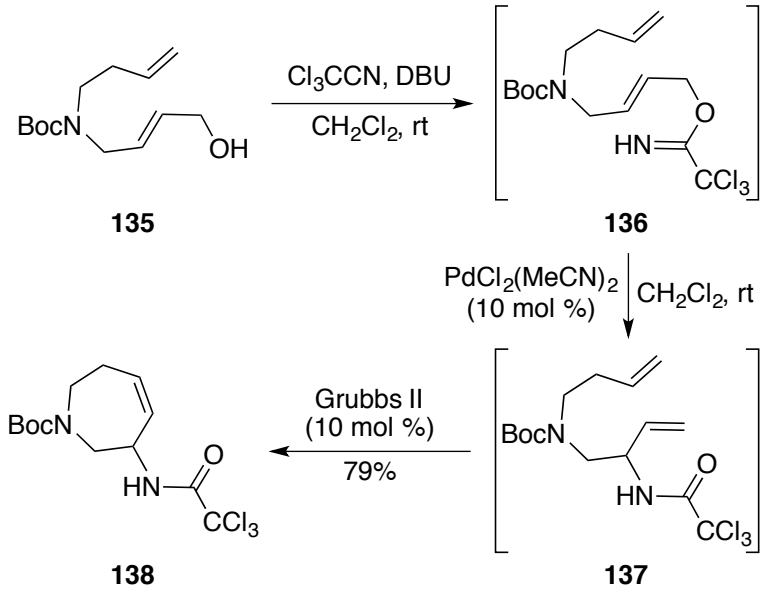
corresponding acids and then selectively cyclised to form the lactone and lactam rings of **133**. Further transformations to install the third ring completed the synthesis of (–)-stemoamide (**134**).



Scheme 35: Development of a one-pot Overman/Johnson-Claisen rearrangement for the synthesis of (–)-stemoamide (134).

Within the Sutherland group, a number of previous projects have focused on the development of one-pot processes involving Overman rearrangement in combination with ring closing metathesis (RCM) or ring closing enyne metathesis (RCEYM) reactions for the synthesis of biologically active compounds and other important synthetic intermediates.[74] One of these was the synthesis of 3-aminoazepane **138** using a one-pot three-step process (Scheme 36).[75] Allylic alcohol **135** (with alkene side chain) was first converted into allylic trichloroacetimidate **136** and then subjected to the Pd-catalysed Overman rearrangement to furnish diene **137**. This was followed by RCM using Grubbs second-generation catalyst to give 2,3,6,7-tetrahydro-3-amidoazepine **138** in 79% overall yield. With the use of chiral palladium catalysts (**56** and **57**) the 3-

aminoazepane **138** was generated in high yields (92%) and high enantioselectivities (92% ee).



Scheme 36: One-pot three-step synthesis of 3-aminoazepane 138.

1.3.5 One-pot process initiated by metathesis reaction

The ruthenium-catalysed reactions, which are mostly based on metathesis, have emerged as important tools in organic synthesis for the construction of new carbon−carbon bonds. Since the discovery of molybdenum and ruthenium complexes (Figure 5) by Schrock and Grubbs in the early 1990's,[76–78] reactions such as ring-opening metathesis (ROM), cross-metathesis (CM), ring-closing metathesis (RCM) and ring-closing enyne metathesis (RCEYM) have been extensively used in the total synthesis of natural products and medicinally important compounds.[79–82] The products generated from the metathesis reactions are well-known precursors for a number of transformations such as olefin hydrogenation, olefin dehydrogenation, olefin isomerisation, cycloaddition, cyclopropanation, cyclisation and others.[59,83–89] Therefore, due to the ability of ruthenium complexes to also catalyse these transformations, the metathesis products could be combined with these reactions in one-pot processes.

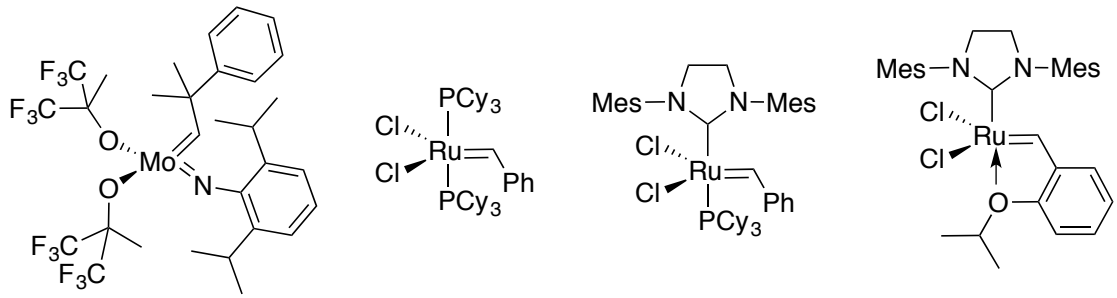
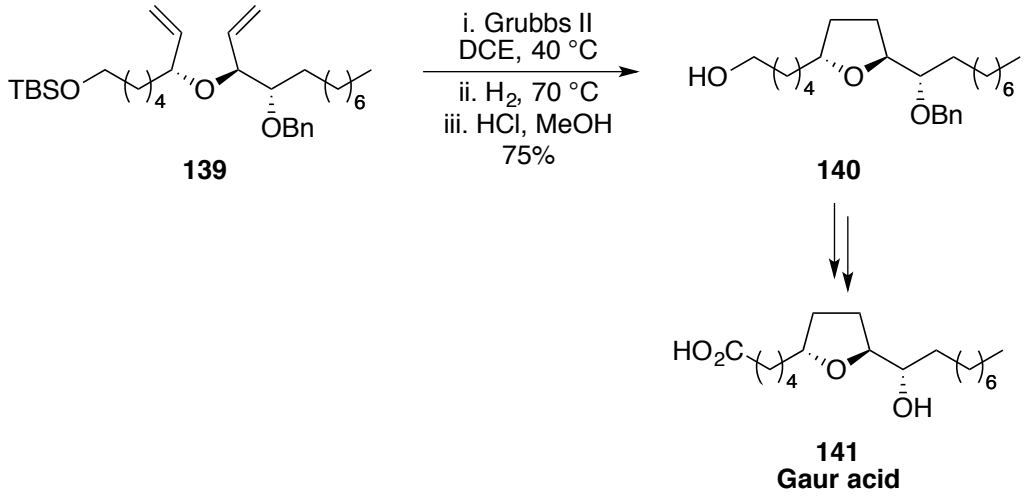


Figure 5: Structures of Schrock and Grubbs catalysts.

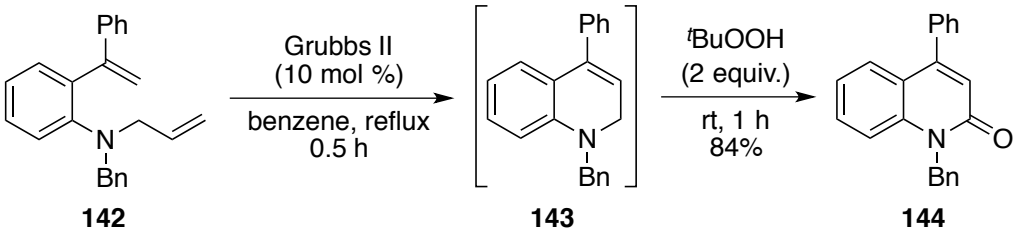
An example of this was used in the synthesis of gaur acid (**141**).[90] Evans and co-workers reported the synthesis of **140** using a one-pot RCM/hydrogenation process (Scheme 37). The RCM of diene **139** with Grubbs second-generation catalyst afforded the desired cyclic ether. Subsequent hydrogenation with addition of H_2 at 70 °C followed by deprotection of TBS group gave product **140** in 75% yield.



Scheme 37: One-pot RCM/hydrogenation process for the synthesis of gaur acid (141).

In 2011, Shuto and co-workers reported a one-pot RCM/oxidation process for the synthesis of 2-quinolone **144** (Scheme 38).[91] Diene **142** was subjected to a RCM reaction using Grubbs second-generation catalyst to obtain 1,2-dihydroquinoline **143**. Treatment of **143** with *tert*-butyl hydroperoxide produced 2-quinolone **144** in 84% yield. To study the effect of ruthenium catalyst on the oxidation reaction, dihydroquinoline **143** was isolated and subjected to the oxidation conditions.

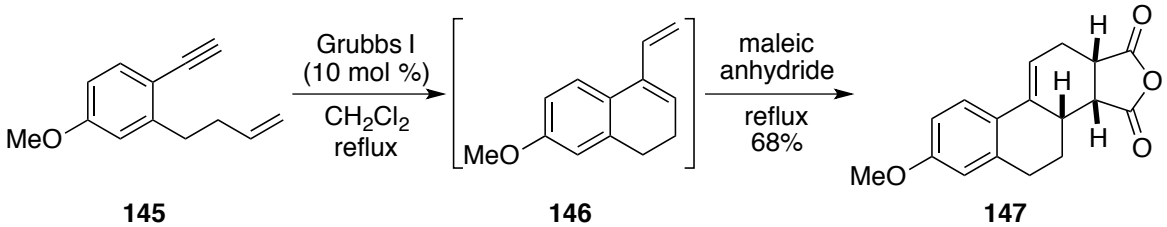
However, this attempt failed to give any quinolone product **144**. This suggested that the presence of ruthenium catalyst was essential to effect the oxidation step. This may due to the conversion of the ruthenium catalyst to another active species, which assisted the oxidation reaction.



142 **143** **144**

Scheme 38: One-pot RCM/oxidation process for the synthesis of 2-quinolone 144.

Enyne metathesis is one of the main types of olefin metathesis. It was described as a bond reorganisation reaction, in which all atoms of the starting material are present in the final product, thus it is an economical process.[92] In enyne metathesis, the combination of both alkyne and alkene species generates a new functionality, a 1,3-diene, which is a useful intermediate that can be used in a wide range of applications. A number of reports have shown that this 1,3-diene can be combined with other reactions (e.g. Diels-Alder) in one-pot tandem processes. This was demonstrated by Pérez-Castle and co-workers who developed a one-pot RCEYM/Diels-Alder reaction for the construction of polycyclic frameworks.[93] Enyne **145** was subjected to a RCEYM reaction to generate the 1,3-diene **146** which was reacted with maleic anhydride in a one-pot process to produce the *endo*-Diels-Alder product **147** in 68% overall yield (Scheme 39).

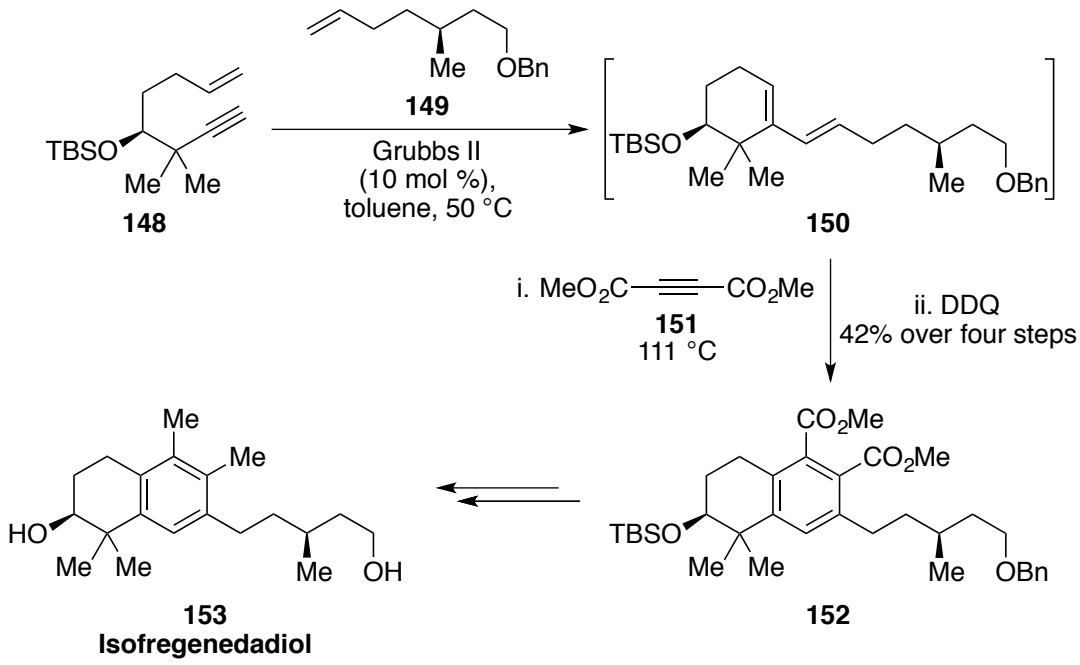


145 **146** **147**

Scheme 39: One-pot RCEYM/Diels-Alder reaction.

An example of utilising the 1,3-diene product in a tandem one-pot process involving an intermolecular cross-metathesis reaction followed by a Diels-Alder reaction and then an aromatisation reaction was reported by Reddy and co-

workers for the synthesis of the natural product, isofregenedadiol (**153**) (Scheme 40).[94] By subjecting 1,7-enyne **148** to a tandem RCEYM/cross metathesis process using olefin **149** as a cross-metathesis partner, the 1,3-diene **150** was generated. This was followed by the addition of alkyne dienophile **151** to form the Diels-Alder product which was then aromatised using DDQ to give the desired polycycle product **152** in 42% overall yield.



Scheme 40: One-pot four-step process involving RCEYM/cross-metathesis reaction followed by a Diels-Alder and then aromatisation reactions for the synthesis of 153.

1.3.6 Conclusions

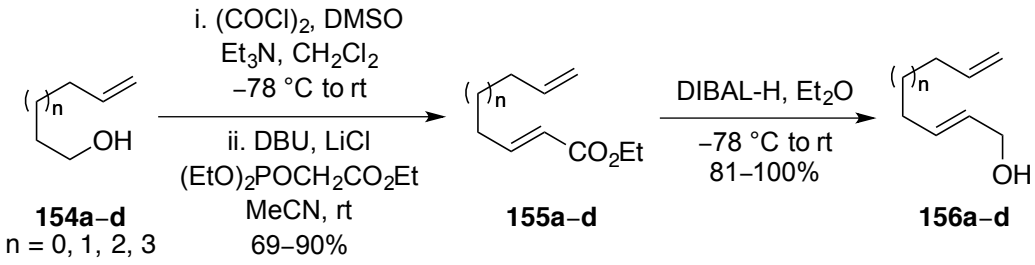
One-pot multi-step processes (domino, cascade, tandem or classical one-pot synthesis) are highly effective methods for the synthesis of highly functionalised molecules from simple and readily available starting materials. Carrying out a number of transformations in the same reaction vessel without isolation and purification of intermediates has a number of advantages over step-wise methods. These include the reduction of the amount of reagents and solvents and other chemical waste, which lead to more friendly methods to the environment. Many of these methods also allow the more efficient synthesis of target compounds compared to step-wise approach.

2.0 Results and Discussion

2.1 One-Pot multi-bond forming reactions for the diastereoselective synthesis of aminobicyclo[4.3.0]nonanes

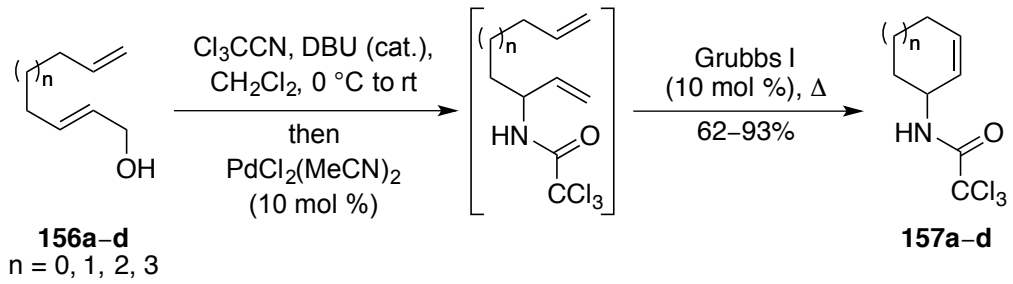
2.1.1 Previous work within the Sutherland group

In order to develop efficient methods for the synthesis of important organic compounds and their intermediates, one-pot multi-bond forming reactions have been an area of interest in the Sutherland research group over the past decade.[74,95–101] In particular, the focus has been on development of one-pot processes involving Overman rearrangements in combination with ring closing metathesis (RCM) or ring closing enyne metathesis (RCEYM) reactions, followed by Diels-Alder reaction. In 2007, the group published the first example of a one-pot Overman rearrangement/RCM process for the diastereoselective synthesis of different cyclic allylic amides from readily available alkene derived allylic alcohols.[95] The required allylic alcohol substrates were prepared in a three-step route from commercially available alken-1-ols **154a**–**d** (Scheme 41). These alken-1-ols substrates **154a**–**d** were first converted to (*E*)-α,β-unsaturated esters **155a**–**d** *via* a one-pot Swern oxidation and a Horner-Wadsworth-Emmons (HWE) reaction. The combination of both reactions in a one-pot process allowed the formation of esters **155a**–**d** in high yields, and this was due to avoiding the isolation of the volatile aldehyde intermediate as well as using the mild Masamune–Roush conditions for the HWE reaction. Reduction of the resulting esters **155a**–**d** with DIBAL-H gave allylic alcohols **156a**–**d** in excellent yields.



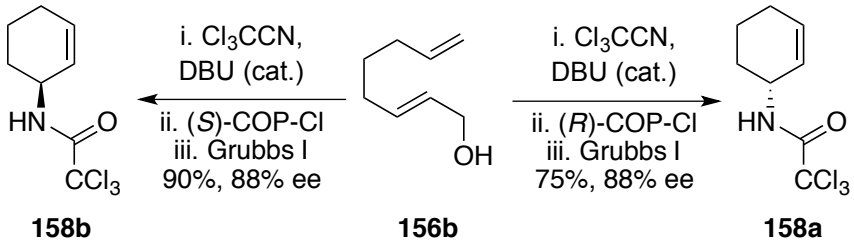
Scheme 41: Synthesis of allylic alcohols 156a–d.

Treatment of allylic alcohol precursors **156a–d** with trichloroacetonitrile and a catalytic amount of DBU afforded the corresponding allylic trichloroacetimidates (Scheme 42). These allylic trichloroacetimidates were then subjected to palladium(II)-catalysed Overman rearrangements followed by ring-closing metathesis reactions to synthesise a small library of five-, six-, seven- and eight-membered cyclic trichloroacetamides **157a–d** in high yields over the three-step processes.[95]



Scheme 42: First developed one-pot synthesis of carbocyclic amides 157a–d.

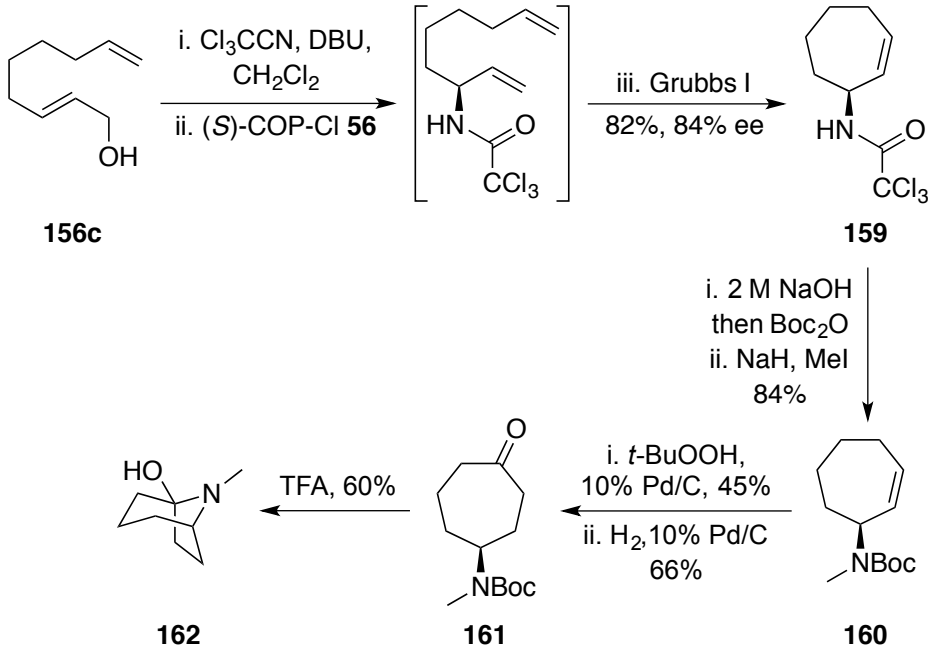
In order to develop a general procedure that can be used in the synthesis of natural products, further work showed that an asymmetric version of the one-pot process could be achieved.[95] For example, the use of chiral palladium catalysts such as (*S*)-COP-Cl **56** and (*R*)-COP-Cl **57** for the Overman rearrangement step allowed stereoselective synthesis of cyclic amide analogues **158a** and **158b** in high yields and enantiomeric excesses (Scheme 43).



Scheme 43: Asymmetric one-pot synthesis of cyclic amide analogues 158a and 158b using chiral palladium catalysts 56 and 57.

Following the successful development of the one-pot two step process, the group applied this methodology to the stereoselective preparation of the natural product, (+)-physoperuvine (**162**).[96] The synthesis began with the conversion of allylic alcohol **156c** to the corresponding allylic trichloroacetimidate (Scheme 44). This

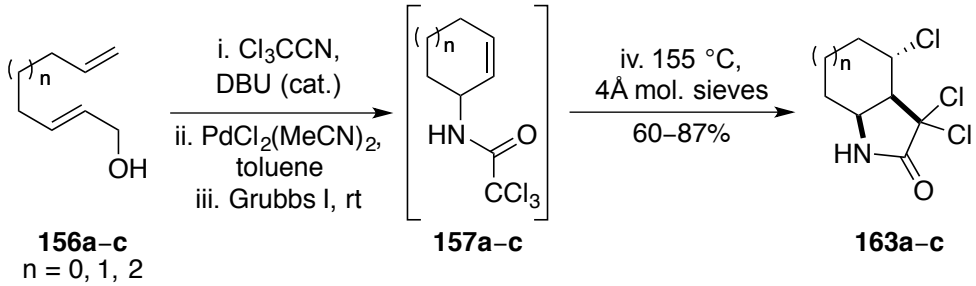
was then subjected to a one-pot asymmetric Overman rearrangement/RCM reaction to give the desired cycloheptyl amide **159** in 82% yield and 84% ee. With the present trichloroacetyl-protecting group, the methylation of **159** was unsuccessful. Therefore, the amine of **159** was reprotected as a Boc-carbamate in a one-pot reaction, and then methylated to give **160** in 84% yield. Allylic oxidation of **160** gave the corresponding α,β-unsaturated ester. This was followed by hydrogenolysis of the alkene to afford the desired oxo-carbamate **161** in a good yield. Finally, the total synthesis of (+)-physoperuvine **162** was completed with amine deprotection of **161** under acidic conditions, which allowed cyclization to the final product.



Scheme 44: Asymmetric synthesis of (+)-physoperuvine (162) using one-pot multi-reaction process.

This methodology was further extended to present a four-step sequence of the one-pot process for the synthesis of more-complex bicyclic systems. For example, bicyclic γ-lactams **163a**–**c** were synthesised in high yields through a one-pot four-step tandem process involving palladium(II)-catalysed Overman rearrangement, RCM and Kharasch cyclisation (Scheme 45).[97] The synthesis began as described in Scheme 42 to form the carbocyclic amides **157a**–**c**, which were then cyclised by Ru(II)-Kharasch reaction to form the desired products **163a**–**c**. The use of chiral

palladium catalysts allowed the asymmetric formation of these bicyclic γ-lactams in excellent enantioselectivites.[98]



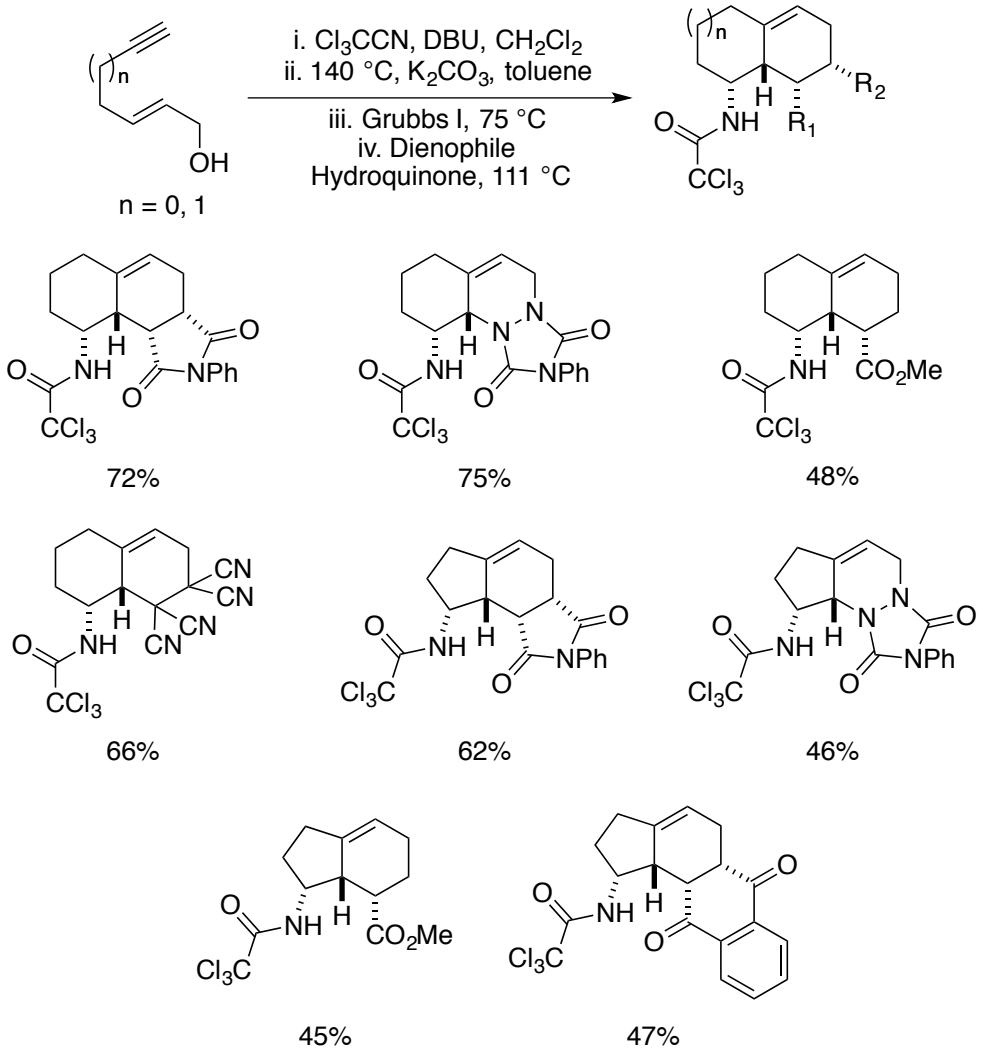
156a–c
n = 0, 1, 2

157a–c

163a–c

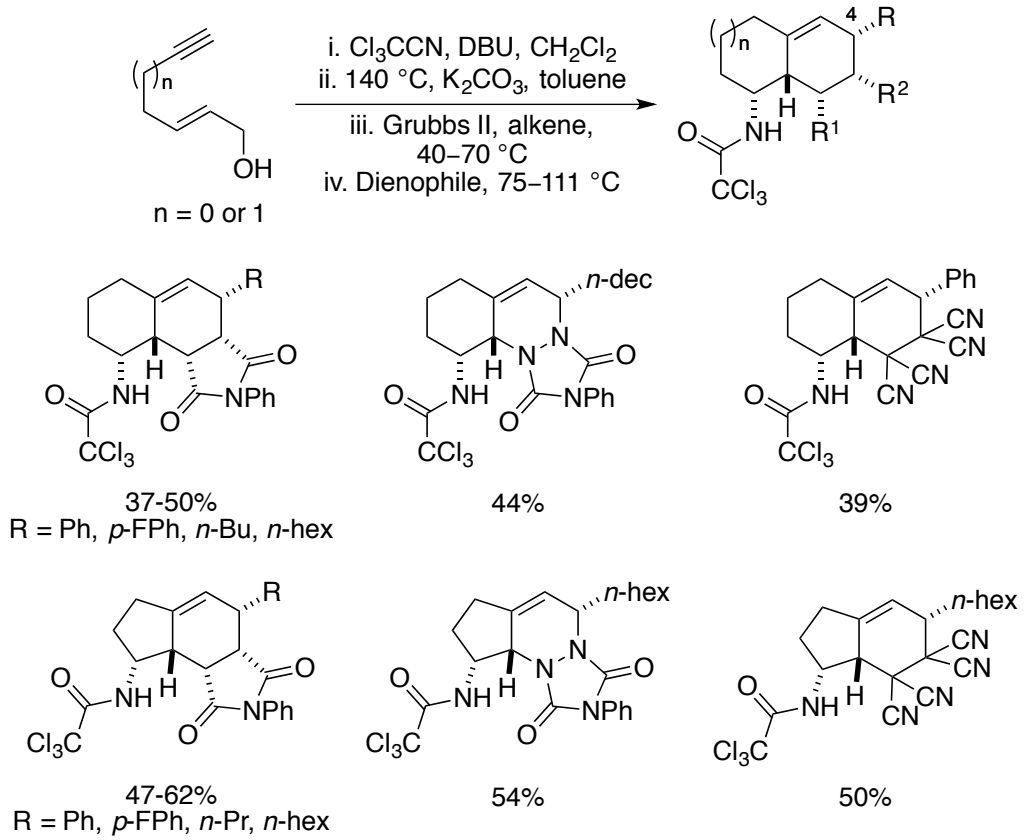
Scheme 45: One-pot tandem process for the synthesis of bicyclic γ-lactams 163a–c.

In 2012, the Sutherland group developed another efficient one-pot four-step process involving a thermal Overman rearrangement, RCEYM reaction, and Diels-Alder reaction for the diastereoselective synthesis of various amino-substituted multi-cyclic scaffolds (Scheme 46).[99] The one-pot processes were performed using readily available allylic alcohols bearing alkyne side-chains. These allylic alcohols were first converted to the corresponding alkyne-derived allylic trichloroacetimidates, which then underwent a one-pot thermal Overman rearrangement followed by a RCEYM reaction to form the corresponding cyclic *exo*-diene. Finally, a hydrogen bond directed Diels-Alder reaction of the formed diene with various dienophiles gave a small library of amino substituted bicyclo[4.4.0]decanes and bicyclo[4.3.0]nonanes in good yields over the four-step process.



Scheme 46: Development of a one-pot four-step process for the synthesis of amino substituted bicyclo[4.4.0]decanes and bicyclo[4.3.0]nonanes scaffolds.

More recently, the group expanded the scope of this process and developed a one-pot five-step tandem process to include a cross metathesis step, resulting in the formation of a library of C-4 substituted polycyclic compounds in good overall yields, using different dienes for the cross metathesis step and different dienophiles for the Diels-Alder reaction (Scheme 47).[101] Interestingly, all products, with up to five stereogenic centres, were isolated as single diastereomers.

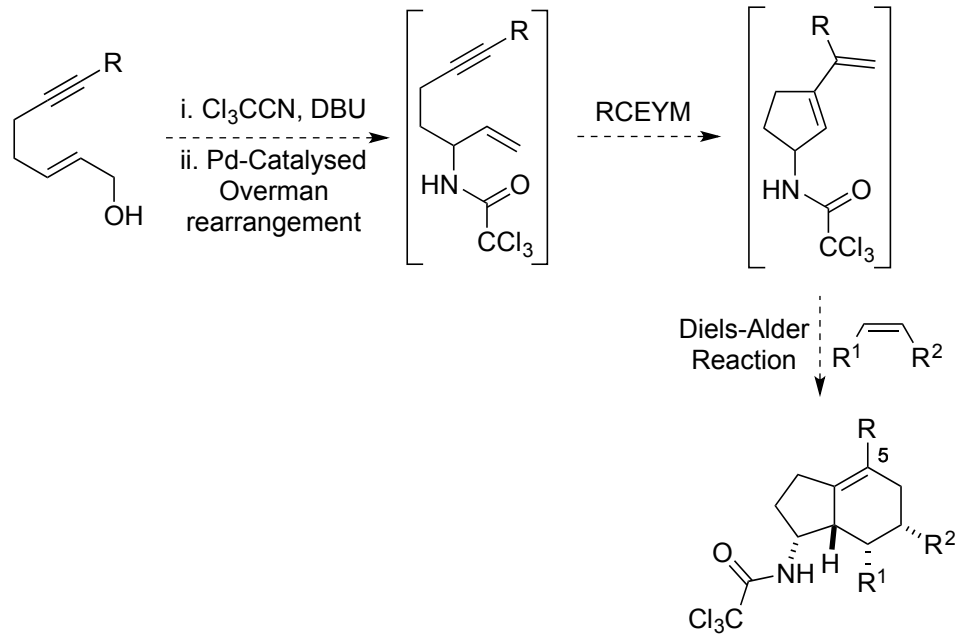


Scheme 47: One-pot tandem process synthesis of C-4 substituted bicyclo[4.4.0]decanes and bicyclo[4.3.0]nonanes.

2.1.2 Aims

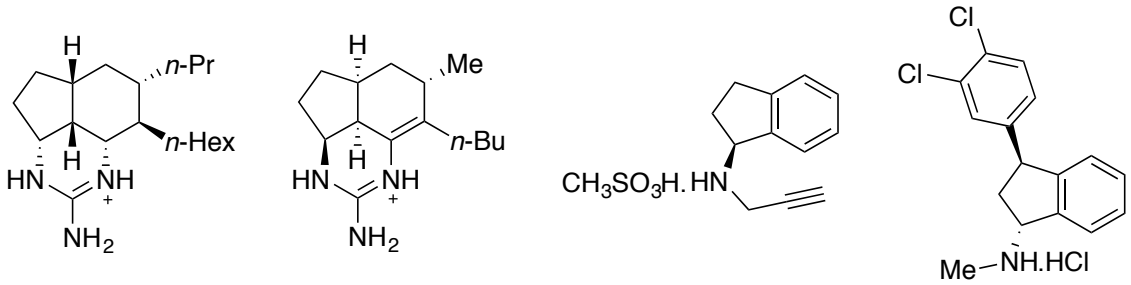
The aim of this project was to extend and explore the previously developed one-pot four-step process to involve a Pd-catalysed Overman rearrangement in place of the thermal rearrangement, to enable diastereoselective and stereoselective synthesises of highly substituted aminobicyclo[4.3.0]nonanes (Scheme 48). From the previously mentioned studies (Scheme 46 and 47), it was found that some of these one-pot reactions required harsher conditions (140 °C) and slightly longer reaction times (36 h) due to the difficulty of the thermal Overman rearrangement. Previous studies in the group showed the feasibility of the palladium(II)-catalysed Overman step for the mono-substituted alkyne derived allylic trichloroaceimidate (R = H). However, due to the palladium binding to the alkyne moiety, the reaction was slow and gave a low yield. Therefore, it was proposed that the use of disubstituted alkynes with bulkier substituents would hinder the alkyne binding to the catalyst, allowing effective palladium catalysis of the Overman rearrangement

to take place. This would lead to the formation of a new library of C-5 substituted aminobicyclo[4.3.0]nonanes with range of substituents. Another aim of this project was to investigate the effects of electronic properties of the alkyne substituents on the outcome of the one-pot process. Finally, the development of a one-pot process, involving a Pd-catalysed Overman rearrangement, would allow asymmetric synthesis of these compounds using chiral palladium catalysts such as (*S*)-COP-Cl **56** and (*R*)-COP-Cl **57**.



Scheme 48: Proposed one-pot process involving a Pd(II)-catalysed Overman rearrangement.

On development of an asymmetric one-pot process, this would allow the preparation of saturated and partially saturated bicyclic nonanes that have found widespread applications due to their biological activities. In particular, amino substituted bicyclo[4.3.0]nonanes are of interest, because they can be found in wide range of natural products and medicinally important compounds. Examples include the guanidine alkaloid, netamine A (**164**),[102] (+)-ptilocaulin (**165**),[103] which is an antitumour antibiotic, rasagiline (**166**),[104] a compound used for the treatment of Parkinson's disease and (+)-indatraline (**167**),[105] a monoamine transporter inhibitor (Figure 6).

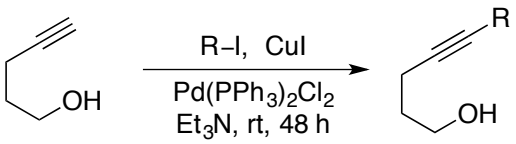


netamine A (**164**) (+)-ptilocaulin (**165**) rasagiline (**166**) (+)-indatraline (**167**)

Figure 6: Examples of biologically active C-1 amino bicyclo[4.3.0]nonanes.

2.1.3 Synthesis of allylic alcohols

The first stage of this project was the preparation of range of disubstituted alkyne derived allylic alcohol precursors to investigate the Pd(II)-catalysed Overman rearrangement. In a four step route, the desired allylic alcohols were synthesised from commercially available pent-4-yn-1-ol (**168**).[106] Firstly, a Sonogashira coupling was used to attach the phenyl group and other derivatives to the alkyne side-chain of pent-4-yn-1-ol (**168**), in the presence of bis(triphenylphosphine)palladium(II) dichloride catalyst (1 mol %) and copper iodide (2 mol %) (Scheme 49). Using iodobenzene as a coupling partner, 5-phenylpent-4-yn-1-ol (**169**) was formed in a 95% yield. To investigate the electronic effects on the one-pot reactions, other disubstituted alkynes bearing electron-rich (*p*-methoxyphenyl) and electron-deficient (*p*-nitrophenyl) groups (**170** and **171**) were also prepared in excellent yields under the same conditions.

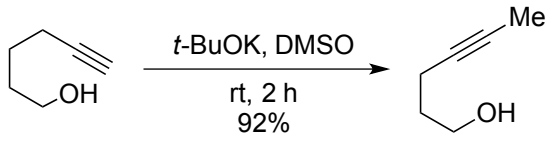


168

169 R = Ph, 95%
170 R = *p*-NO_2Ph, 99%
171 R = *p*-MeOPh, 95%

Scheme 49: Sonogashira reaction for the synthesis of disubstituted alkynes 169–171.

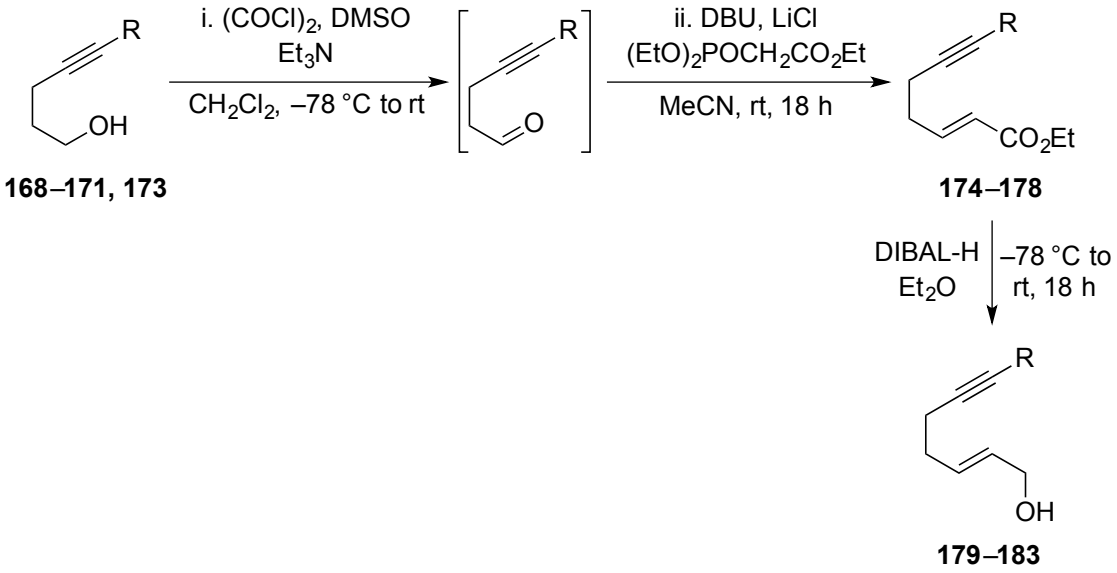
The preparation of alkyl analogue **173** (R = Me) was achieved in 92% yield through an isomerisation reaction of commercially available hex-5-yn-1-ol (**172**) using potassium *tert*-butoxide in dimethyl sulfoxide (Scheme 50).[107]



172 **173**

Scheme 50: Preparation of hex-4-yn-1-ol 173.

As well as the mono-substituted alkyne **168** (R = H), the disubstituted alkynes **169**–**171** and **173** were all subjected to one-pot Swern oxidation/Horner-Wadsworth-Emmons reactions under Masamune–Roush conditions to form the corresponding (*E*)-α,β-unsaturated esters **174**–**178** in almost quantitative yields (Table 4). This one-pot reaction has been developed and successfully utilised in many synthetic transformations within the Sutherland research group.[31,95−97,99−101] In particular, the mild Swern oxidation is useful, because in some cases the aldehyde intermediate is unstable or volatile, and so handling is minimised using the one-pot process. During the HWE transformation, the mild Masamune–Roush conditions are designed for base sensitive substrates. In this reaction, a mild Lewis acid such as lithium chloride is used to increase the acidity of the triethyl phosphonoacetate and therefore a mild base such as 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) can be employed. The use of a stabilised phosphonate ester that reacts with the aldehyde in the presence of lithium chloride gives only *E*-alkenes. The formation of *E*-isomers of all (*E*)-α,β-unsaturated esters formed were analysed by ^{1}H NMR spectroscopy which showed large coupling constants of ~15.7 Hz between the alkene hydrogen atoms. Finally, reduction of esters **174**–**178** with DIBAL-H led to the formation of the desired C-7 substituted hept-2-en-6-yn-1-ols **179**–**183** in excellent yields.



168–171, 173 **174–178** **179–183**

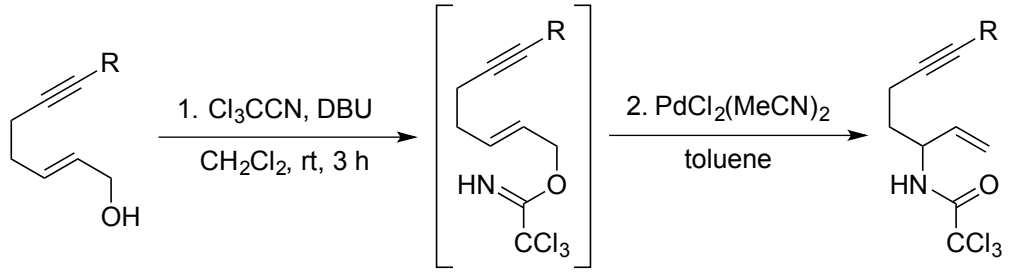
Entry	R	Yield (%)	Yield (%)
1	H, **168**	**174**, 91	**179**, 87
2	Me, **173**	**175**, 95	**180**, 87
3	Ph, **169**	**176**, 95	**181**, 98
4	*p*-NO_2-Ph, **170**	**177**, 95	**182**, 83
5	*p*-MeO-Ph, **171**	**178**, 94	**183**, 94

Table 4: Synthesis of allylic alcohols 179–183.

2.1.4 Investigation of the palladium(II)-catalysed Overman rearrangement

Having the required C-7 substituted hept-2-en-6-yn-1-ols **179–183** in hand, the next stage of this study was to investigate their abilities to undergo a Pd(II)-catalysed Overman rearrangement (Table 5). Initially, the mono-substituted alkyne (2*E*)-hept-2-en-6-yn-1-ol (**179**) was treated with trichloroacetonitrile and a catalytic amount of DBU to form the corresponding allylic trichloroacetimidate. The imidate was then subjected to a Pd(II)-catalysed Overman rearrangement under standard conditions of 10 mol % catalyst loading at room temperature.[108] However, minimal conversion (less than 10 %) to the amide product **184** was observed after 24 h (entry 1). As mentioned earlier, the low conversion was associated with the palladium catalyst binding to the alkyne side-chain. By heating the reaction to 40 °C and adding an extra batch of the catalyst (10 mol %), the amide product **184** was afforded in 34% yield after 48 h (entry 2). The rearrangement using

disubstituted alkyne-derived allylic alcohols **180**–**183** was next investigated. It was notably found that when a small substituent such as the methyl group was attached to the alkyne, the corresponding allylic trichloroacetamide **185** was formed in modest yield at room temperature using only 10 mol % of the catalyst (entry 3). More bulky aryl substituents having different electronic properties were then tested and proved to be more effective, allowing the formation of amides **186**–**188** in high yields and shorter reaction times (entries 4, 5 and 6). From these results, it was proposed that the electronic properties of the substituents have no effects on the reaction outcome, and only steric bulk was responsible for impeding the catalyst binding to the alkyne.



179–**183** **184**–**188**

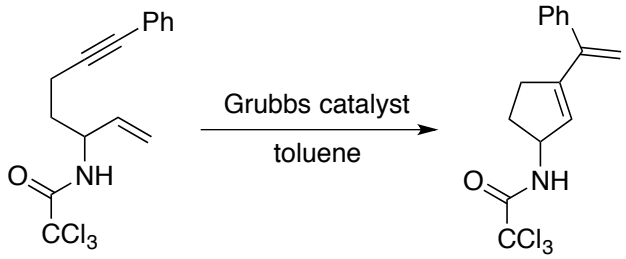
Entry	R	Temp. (°C)	Catalyst load. (mol %)	Time (h)	Yield[a] (%)
1	H, **179**	20	10	24	**184**, <10[b]
2	H, **179**	40	10 + 10	48	**184**, 34
3	Me, **180**	20	10	24	**185**, 55
4	Ph, **181**	20	10	12	**186**, 81
5	*p*-NO_2-Ph, **182**	20	10	12	**187**, 76
6	*p*-MeO-Ph, **183**	20	10	12	**188**, 83

Table 5: Palladium(II)-catalysed Overman rearrangement. [a]Isolated yields from allylic alcohols 179–183, [b]Conversion calculated by ^{1}H NMR spectroscopy of crude reaction mixture.

2.1.5 Development of the one-pot multi-step process

After identifying the optimal conditions for the Pd(II)-catalysed Overman rearrangement step, attention was then turned to the RCEYM reaction. Previous work within the group showed that the RCEYM reaction of the mono-substituted

alkyne could be effectively performed using Grubbs first-generation catalyst to give the desired 1,3-diene with full conversion (Scheme 46).[99] However, preliminary study on the preparation of 1,3-diene **189** using Grubbs first- or second-generation catalysts proved unsuccessful, with the reactions proceeding with low conversions (Table 6, entries 1 and 2).[108] The low reactivity of the Grubbs catalysts was associated with the disubstituent alkyne with a bulky phenyl group attached. A range of conditions were then investigated to optimise the reaction, and the best results were obtained using Grubbs second-generation catalyst (7 mol %) in combination with octa-1,7-diene **190** and an increase of temperature to 90 °C (entry 4).



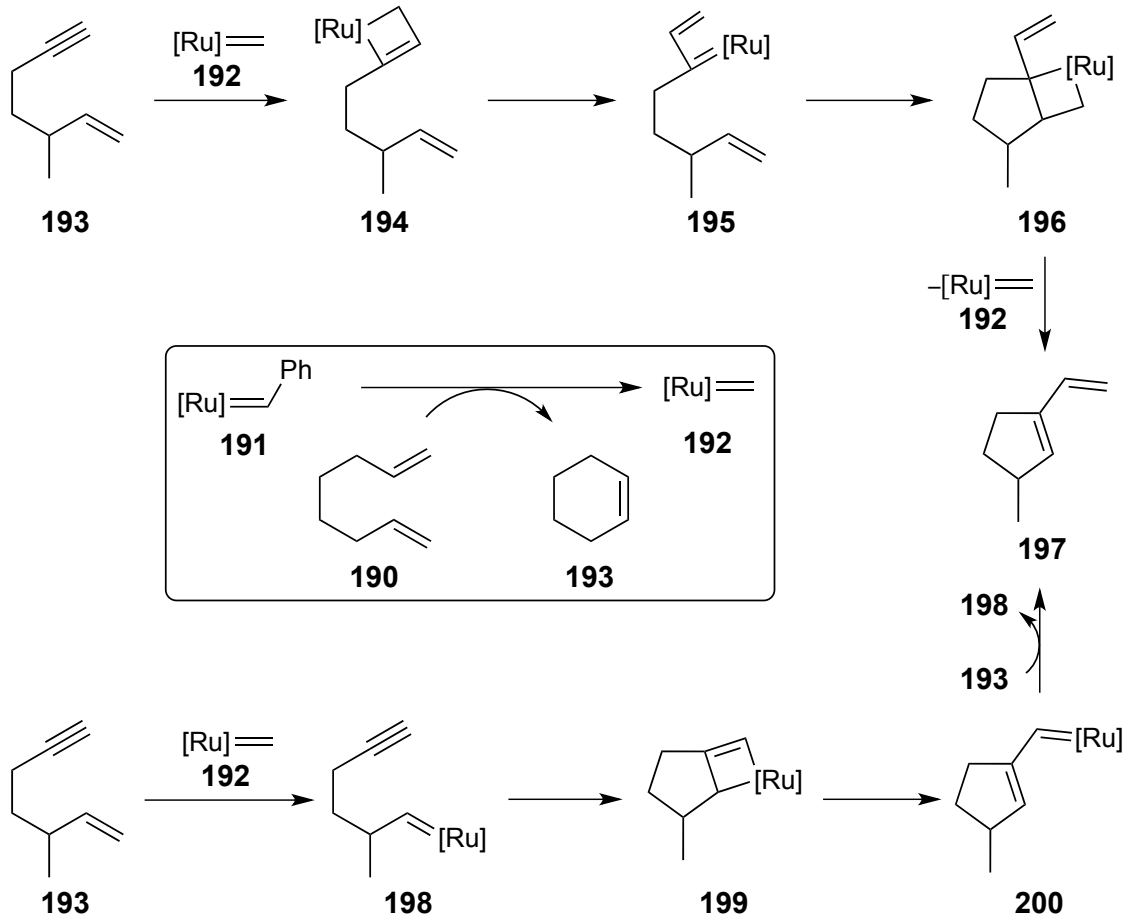
186 **189**

Entry	Catalyst	Loading (mol %)	Additive	Temp. (°C)	Time (h)	Conversion[a] (%)
1	Grubbs 1st	10	-	75	48	<10
2	Grubbs 2nd	10	-	75	48	<20
3	Grubbs 2nd	10	octa-1,7-diene **190**	75	18	100
4	Grubbs 2nd	7	octa-1,7-diene **190**	90	18	100

Table 6: RCEYM reaction for the formation of 1,3-diene 189. [a]Conversion calculated by ^{1}H NMR spectroscopy of crude reaction mixture.

As developed by Fustero *et al*., octa-1,7-diene can be used to accelerate RCEYM reactions by forming ethylene *in situ*.[109] This method is safer than using ethylene gas which is highly flammable and difficult to handle. The possible mechanism of the RCEYM reaction using octa-1,7-diene is shown below (Scheme 51).[110–113] The first stage is a RCM reaction between the ruthenium catalyst **191** and octa-1,7-diene **190** to form the activated ruthenium carbene **192** and cyclohexene **193**. The

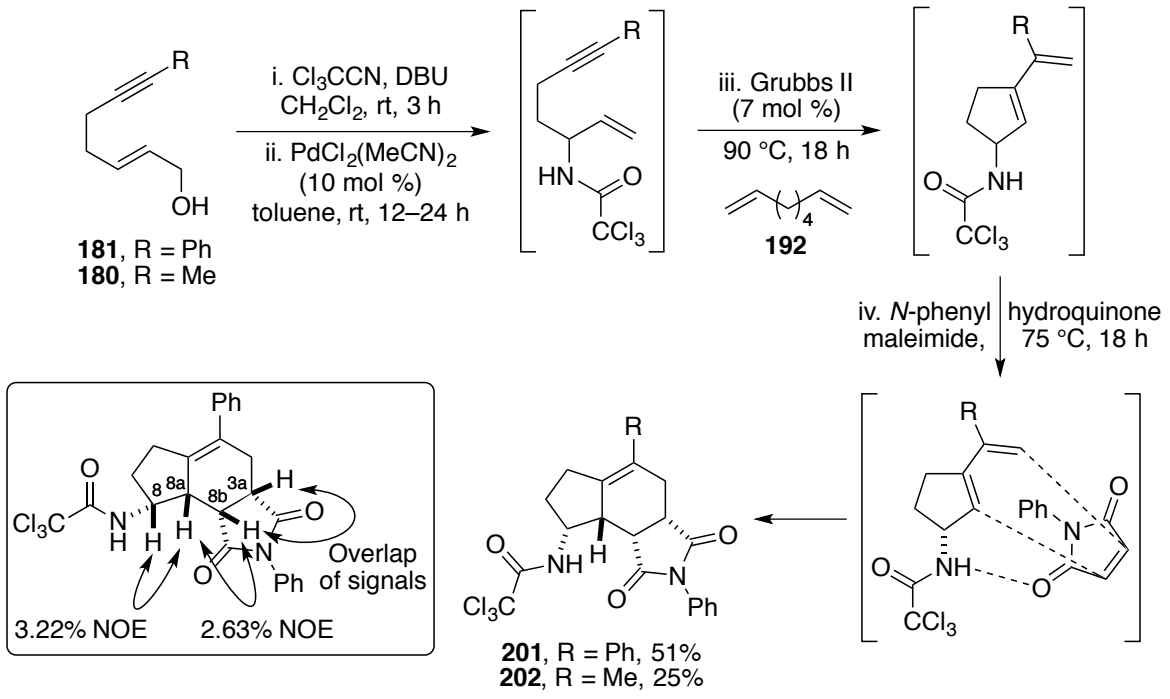
activated ruthenium species **192** can either react with alkyne or alkene moieties, leading to two possible mechanisms. The reaction of ruthenium species **192** with the alkyne side-chain (called 'yne-then-ene pathway') can proceed *via* [2+2] cycloaddition to form ruthenacyclobutene **194**, which then can undergo ring-opening to afford ruthenium carbene complex **195**. This would then react with alkene moiety to produce ruthenacyclobutane **196**. Subsequent ring-opening of **196** gives 1,3-diene (*exo*-product) **197** and the activated ruthenium carbene **192**. In terms of the reaction of **192** with the alkene moiety (called 'ene-then-yne pathway'), the alkylidene **198** would be formed and then undergo a ring closure to generate ruthenacyclobutene **199**. Ring-opening of **199** affords ruthenium carbene **200**. Finally, the reaction of **200** with a second equivalent of **193** leads to the *exo*-product **197** and regeneration of the alkylidene intermediate **198**.



Scheme 51: RCEYM reaction mechanism using octa-1,7-diene.

Using these optimised conditions for both steps, the one-pot four-step process was attempted (Scheme 52). The process was initially performed using alkyne-

derived allylic alcohol **181** with the phenyl group as an alkyne substituent. This allylic alcohol was first treated with trichloroacetonitrile and a catalytic amount of DBU to form the corresponding allylic trichloroacetimidate. This was then subjected to a one-pot Pd(II)-catalysed Overman rearrangement followed by a RCEYM reaction to form the required cyclic *exo*-diene. Finally, a hydrogen bonding directed Diels-Alder reaction of the 1,3-diene with *N*-phenylmaleimide as a dienophile gave the desired amino-substituted bicyclo[4.3.0]nonane **201** in 51% yield as a single diastereomer. During the Diels-Alder reaction, hydroquinone was added to the reaction mixture to prevent radical polymerisation of the dienophile that is known to occur at high temperature.[114,115] The stereochemistry of compound **201** was proven by NOE studies where a *syn* relationship was observed between the hydrogen atoms at C8, C8a, C8b and C3a. In comparison, allylic alcohol **180** with a methyl group attached to the alkyne was subjected to the one-pot process, and gave only a 25% yield of the corresponding bicyclic compound **202**. As mentioned earlier (Table 5, entry 3), this was due to a less efficient Overman rearrangement step.

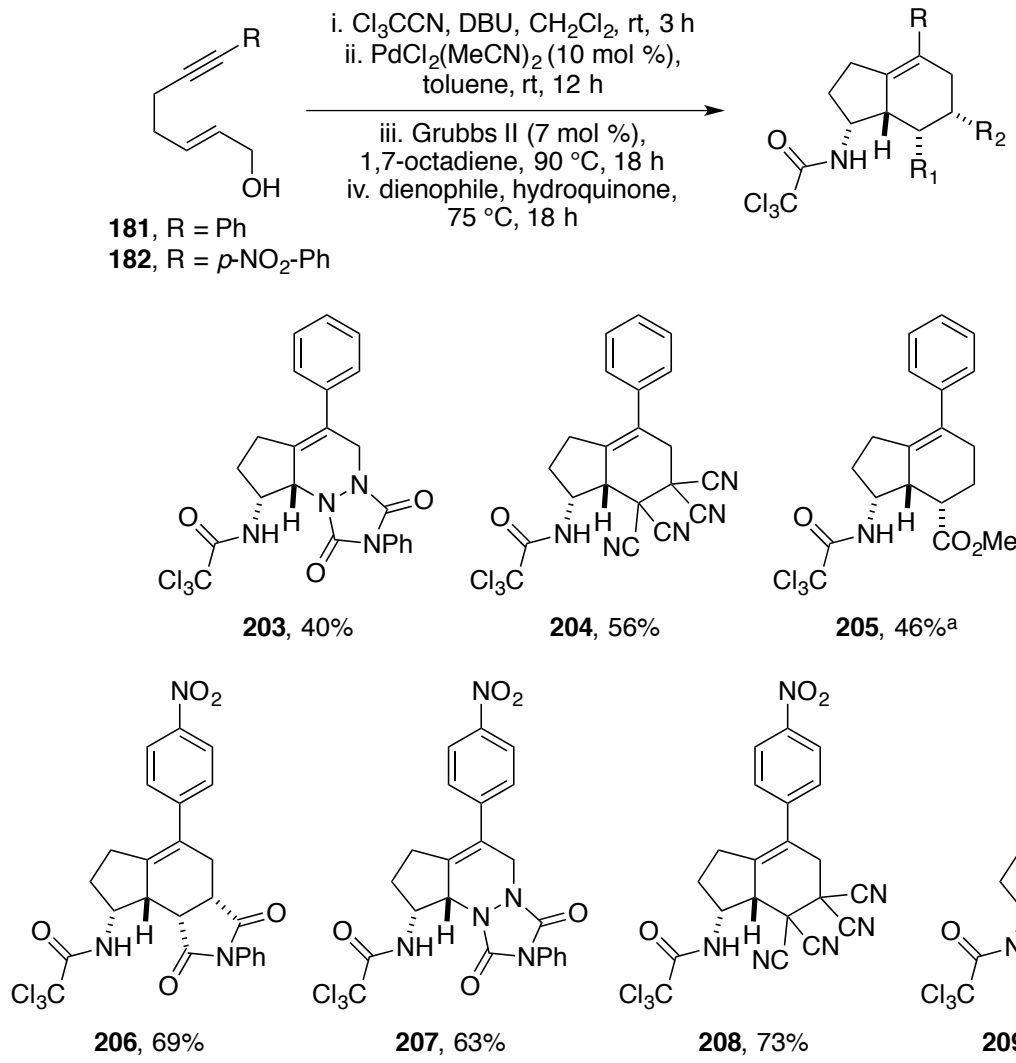


Scheme 52: One-pot four-step process using allylic alcohols 181 and 180.

Having successfully developed the four-step one-pot process for the synthesis of bicyclic compound **201**, the scope of the process was explored. Alkyne-derived

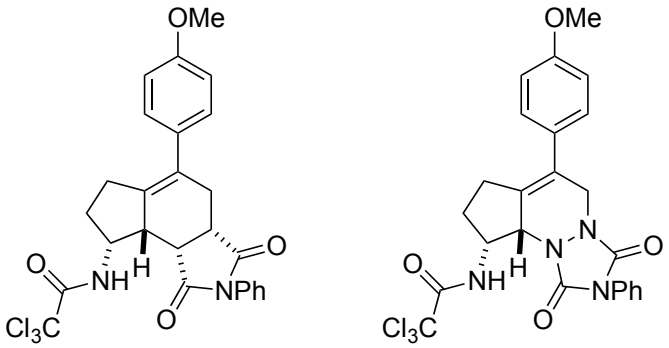
allylic alcohol **181** was further subjected to the one-pot process with the use of other dienophiles for the final Diels-Alder reaction (Scheme 53). With a less reactive diene, it was found that only strongly electron-deficient dienophiles could provide the desired products in good yields. The use of other symmetrical dienophiles such as 4-phenyl-1,2,4-triazole-3,5-dione and tetracyanoethylene allowed the successful synthesis of indane compounds **203** and **204** as single diastereomers in good yields (40% and 65%, respectively). To investigate the compatibility of the one-pot process with other dienophiles, the Diels-Alder reaction using methyl acrylate as a nonsymmetrical dienophile was conducted. This gave the corresponding aminobicyclo[4.3.0]nonane **205** in 46% yield. It is worth noting that compound **205** was isolated as a single regioisomer, and this is a consequence of the Diels-Alder reaction proceeding *via* a hydrogen bonding directed *endo* transition state.

Another important objective of this study was to use alkyne substituents with different electronic properties to investigate this effect on the outcome of the RCEYM step. Alkyne-derived allylic alcohol **182** bearing an electron-deficient aryl group was subjected to the one-pot multi-step process (Scheme 53). Using *N*-phenylmaleimide as a dienophile, the desired 4-nitrophenyl substituted bicyclo[4.3.0]nonane **206** was synthesised as a single diastereomer in 69% yield. Other dienophiles such as 4-phenyl-1,2,4-triazole-3,5-dione, tetracyanoethylene and methyl acrylate were employed in the final Diels-Alder reaction and successfully generated the corresponding 4-nitrophenyl substituted bicyclo[4.3.0]nonanes **207**–**209** in good overall yields (63%, 73% and 46%, respectively). In general, it was found that the electron-deficient allylic trichloroacetamide **187** was able to undergo a more effective RCEYM reaction under these conditions. This is due to the presence of the electron withdrawing *p*-NO_2-group enhancing the reaction between the alkyne component and the electron rich Ru-alkylidene.



Scheme 53: Synthesis of a library of phenyl and 4-nitrophenyl substituted bicyclo[4.3.0]nonanes 203–209 through one-pot multi-step processes. [a]Diels-Alder reaction was performed at 111 °C for 5 days.

In comparison, when electron-rich (2*E*)-7-(4'-methoxyphenyl)hept-2-en-6-yn-1-ol (**183**) was employed in the one-pot process under the same conditions using *N*-phenylmaleimide and 4-phenyl-1,2,4-triazole-3,5-dione as dienophiles, low yields were obtained for the corresponding 4-methoxyphenyl substituted bicyclo[4.3.0]nonanes **210** and **211** (Figure 7).



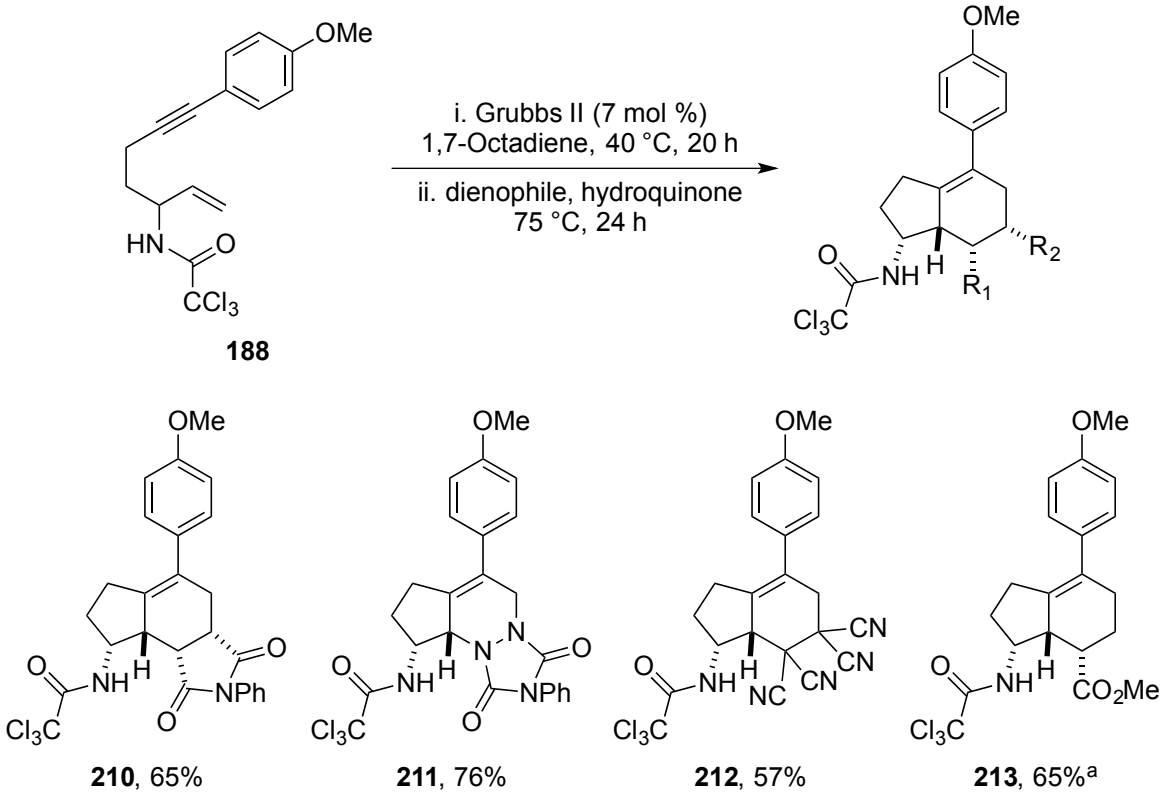
210, 34% **211**, 23%

Figure 7: 4-Methoxyphenyl substituted bicyclo[4.3.0]nonanes 210 and 211.

Reactions of the one-pot process involving allylic alcohol **183** were then re-investigated to ensure each step went to completion. As mentioned in Table 5, allylic alcohol **183** underwent an efficient one-pot Pd-catalysed Overman rearrangement and gave the allylic amide **188** in 83% yield. In this case, it seemed that the problem was associated with the RCEYM reaction as there should not be any problem with a Diels-Alder reaction of an electron-rich diene with electron deficient dienophiles. Analysis of the ^{1}H NMR spectrum of the crude RCEYM reaction showed that the cyclopentyl *exo*-diene compound was successfully formed. However, it seemed that the high temperature (90 °C) of the RCEYM reaction resulted in partial decomposition of this highly reactive diene.

The RCEYM reaction of the 1,6-enyne **188** was then reinvestigated with Grubbs second-generation catalyst and octa-1,7-diene at various temperatures. It was found that the reaction went to completion after 18 h at much lower temperature of 40 ºC. To avoid any issues during the purification step, it was proposed that the Diels-Alder reaction could take place in the same pot. *N*-Phenylmaleimide was then added and the reaction mixture was stirred for 24 h at 75 ºC, giving the desired product **210** in 65% yield (Scheme 54). Under these optimised conditions of the low temperature RCEYM step, allylic alcohol **183** was re-subjected to the one-pot four-step process. However, all attempts ended with low yields. Therefore, with this particular analogue, it was decided that the synthesis of **210**–**213** would be carried out using two separate one-pot processes. Initially, imidate formation and then a Pd(II)-catalysed Overman rearrangement was used to form the allylic trichloroacetamide **188**. Using various electron-deficient dienophiles, the allylic

trichloroacetamide **188** was then subjected to a one-pot two-step process involving the RCEYM and Diels-Alder reactions. This allowed the formation of 4-methoxyphenyl substituted bicyclo[4.3.0]nonanes **210**–**213** in good overall yields.

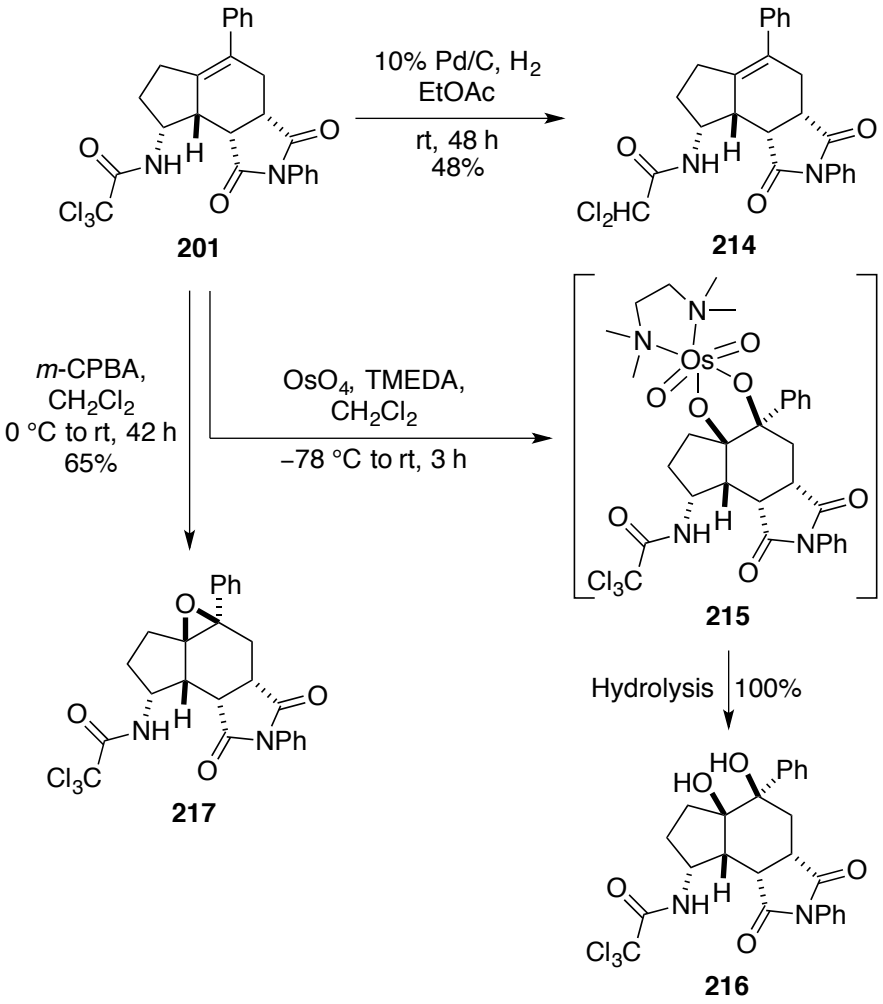


Scheme 54: One-pot two-step synthesis of 4-methoxyphenyl substituted bicyclo[4.3.0]nonanes 210–213. [a]Diels-Alder reaction was performed at 111 °C for 5 days.

2.1.6 Functionalisation of bicyclo[4.3.0]nonane 201

After the success of the one-pot process for the synthesis of a novel library of bicyclo[4.3.0]nonanes, the next aim was to explore functionalisation of these compounds. Initial efforts were made to reduce the alkene of bicyclo[4.3.0]nonane **201** using 10% palladium on carbon under an atmosphere of hydrogen. Unfortunately, this attempt failed and only 71% conversion to the dichloroacetamide **214** was observed (48% isolated yield) (Scheme 55). It was proposed that this was due to the hindered nature of the tetra-substituted alkene. Although the reduction of **201** was challenging, oxidation of the alkene was successful. For example, dihydroxylation of compound **201** under Donohoe's conditions,[116,117] using osmium tetroxide and *N*,*N*,*N*′,*N*′-

tetramethylethylenediamine (TMEDA) in dichloromethane at –78 °C gave dihydroxy derivative **216** as a single diastereomer in quantitative yield. In this method, the combination of TMEDA and OsO_4 is used to enhance the reactivity of the catalyst by forming a more electron-rich bidentate complex. This newly formed complex then reacted with the alkene of **201** to form the osmate ester **215** which after hydrolysis gave the desired dihydroxylated product **216**. Based on the curved shape of **201**, it was expected that the catalyst would attack from the less hindered top face of the molecule. In a similar way, an epoxidation reaction of amino bicyclo[4.3.0]nonane **201** with *meta*-chloroperoxybenzoic acid (*m*-CPBA) gave epoxide **217** in 65% yield. The epoxide derivative **217** was formed as major diastereomer in a 4:1 ratio.



Scheme 55: Reduction, dihydroxylation and epoxidation reactions of aminobicyclo[4.3.0]nonane 201.

The relative stereochemistry of the dihydroxy product **216** was confirmed by X-ray crystallography (Figure 8). The X-ray structure also proved the relative stereochemistry of the product of the one-pot process **210**, and showed the *syn* relationship of the hydrogen atoms around the stereogenic centres.

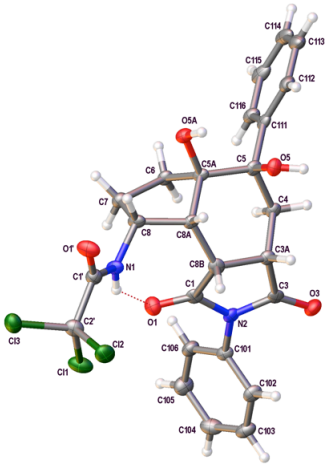


Figure 8: View showing the structure of one of the crystallographically independent molecules of 216.

2.1.7 Conclusions

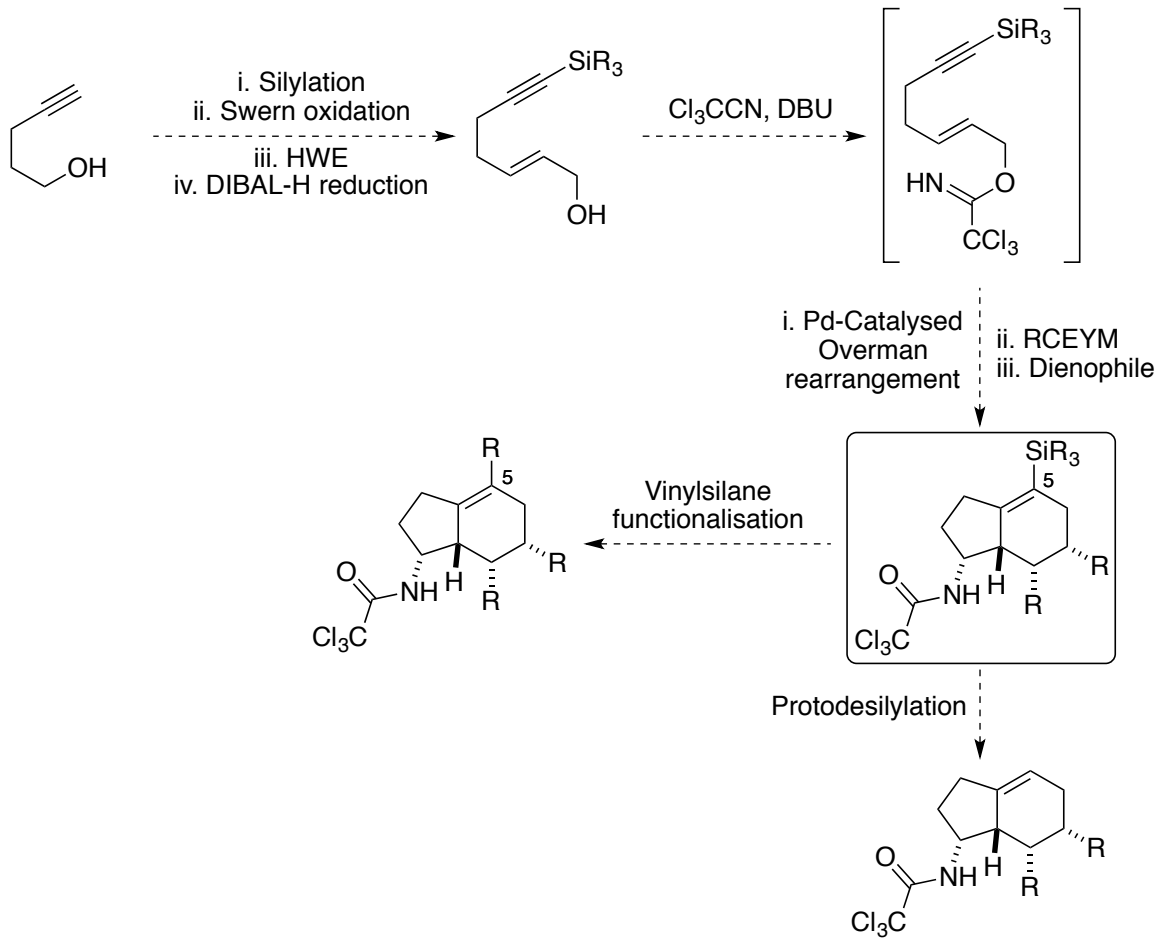
In conclusion, a library of C-5 substituted aminobicyclo[4.3.0]nonanes has been successfully prepared through a one-pot four-step process involving Pd(II)-catalysed Overman rearrangement, Ru(II)-catalysed RCEYM and hydrogen bonding Diels-Alder reactions. The study began with the preparation of series of disubstituted alkyne-derived allylic alcohols using a one-pot Swern oxidation and HWE reaction as the key steps. These compounds were then used to investigate the palladium catalysis of the Overman rearrangement and then utilised in a one-pot multi-step process. The effect of the electronic properties of the aryl substituents on the outcome of the one-pot process was also examined. The electron-deficient 4-nitrophenyl analogue proved to be an effective substrate enabling the synthesis of the corresponding aminobicyclo[4.3.0]nonanes in high overall yield. On the other hand, the electron-rich 4-methoxyphenyl analogue underwent partial decomposition during the RCEYM reaction at high temperature. To overcome this issue, the synthesis of 4-methoxyphenyl substituted bicyclo[4.3.0]nonanes were carried out in two separate one-pot processes. Finally, the phenyl substituted bicyclo[4.3.0]nonane analogue was further functionalised

yielding highly substituted sp^3-rich, polycyclic scaffolds with up to six stereogenic centres.

2.2 The development of a one-pot process for the synthesis of vinylsilyl derived aminobicyclo[4.3.0]nonanes, synthetic intermediates for a late-stage incorporation of substituents

2.2.1 Aims

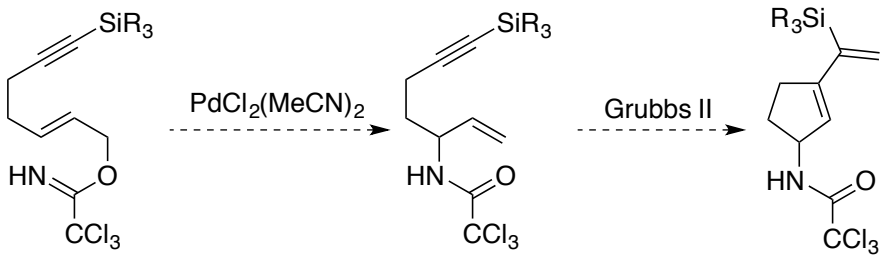
As described in the previous section, a one-pot multi-bond forming process has been successfully developed for the synthesis of a library of C-5 substituted aminobicyclo[4.3.0]nonanes **201**–**213** in good yields. This study has clearly shown that the presence of simple aryl groups was necessary to block the alkyne and allow an effective Pd(II)-catalysed Overman rearrangement to proceed under mild conditions. Also, the use of a disubstituted alkyne did not significantly retard the following RCEYM reaction. However, the C-5 structural diversity of these compounds was introduced *via* a Sonogashira cross coupling during the first step. This required the formation of a series of disubstituted alkynes from the first step and for each of them to be transformed through the entire route to each final compound. To overcome this limitation, the aim of this project was to incorporate an alkyne substituent that would allow the late-stage introduction of groups at C-5. It was proposed that a silyl protecting group could facilitate a Pd(II)-catalysed Overman rearrangement and this would be then utilised in a one-pot process including RCEYM and Diels-Alder reactions (Scheme 56). Once the one-pot process has been fully optimised, the C-5 silyl substituted bicyclic product could be functionalised *via* cross coupling reactions such as a Hiyama-Denmark coupling. This would allow the late-stage synthesis of C-5 substituted bicyclo[4.3.0]nonane compounds with a wide range of substituents in a single step. Another objective of using this newly developed process would be removal of the silyl group to allow the formation of the non-substituted analogue.[118]



Scheme 56: **Proposed one-pot synthesis and functionalisation of C-5 substituted aminobicyclo[4.3.0]nonanes.**

In this project, four major factors were considered.

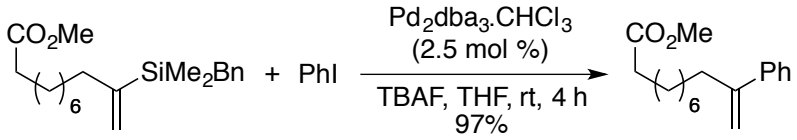
1. The stability of the silyl group for preparation of the allylic alcohol precursor, as well as the conditions of the one-pot multi-step process.
2. The ability of the silyl group to hinder the catalyst binding to the alkyne and facilitate the palladium(II)-catalysed Overman rearrangement (Scheme 57).
3. To be aware that the silyl group may hinder the RCEYM reaction.
4. The reactivity of the vinylsilane functionality towards palladium-catalysed cross-coupling reactions.



Scheme 57: One-pot Pd(II)-catalysed Overman rearrangement/ RCEYM using silyl-derived alkyne.

In recent years, a wide range of silanes have been used in palladium-catalysed cross-coupling reactions and successfully utilised in many important synthetic applications.[119–121] In this project, two different silyl groups were chosen. Initially, the *tert*-butyldimethylsilyl (TBDMS) group will be used to investigate the steric requirements for the one-pot process. Having successfully tested the optimal conditions of the process using the TBDMS group, the synthetic route will then be repeated using benzyldimethylsilyl (BDMS) group, as this group would be stable during the synthesis of the aminobicyclo[4.3.0]nonane, and could be used for Hiyama-Denmark cross-coupling reactions.

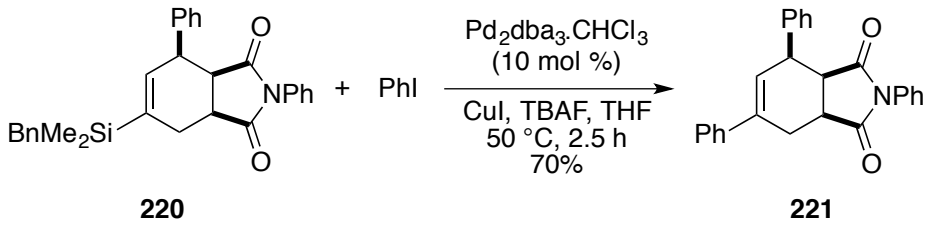
In 2003, Trost and co-workers reported the BDMS group as a suitable coupling partner that can lead to cross-coupled products under mild conditions.[122] For example, treatment of disubstituted vinylsilane **218** and phenyl iodide with *tetra-n*-butylammonium fluoride (TBAF) in the presence of tris(dibenzylideneacetone)dipalladium(0) gave coupled product **219** in 97% yield at room temperature (Scheme 58) . Using various disubstituted vinylsilanes with different electrophilic partners, the scope of this method was explored and resulted in the formation of the corresponding cross-coupled products in high yields.



218 **219**

Scheme 58: A literature example of Hiyama-Denmark coupling of vinylsilyl 218.

In 2010, Junker *et al*. reported another example of using the BDMS group in Hiyama-Denmark coupling reaction.[123] Under similar reaction conditions, compound **220** reacted with iodobenzene and gave product **221** in 70% yield (Scheme 59).



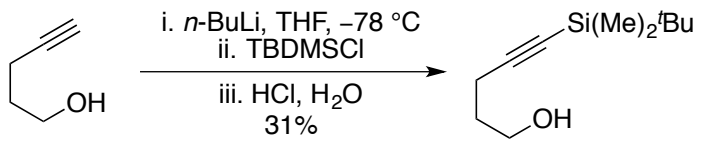
220 **221**

Scheme 59: Formation of 221 *via* Hiyama-Denmark cross-coupling reaction.

2.2.2 Development of a one-pot process using a *tert*-butyldimethylsilylalkynyl-derived allylic alcohol

2.2.2.1 Synthesis of allylic alcohol

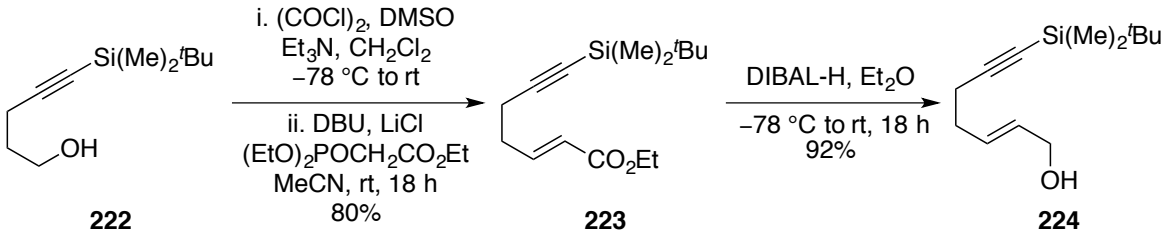
The synthetic route began with the conversion of pent-4-yn-1-ol (**168**) to its *C*-silylated derivative **222**, using *n*-butyllithium and two equivalents of *tert*-butyldimethylsilyl chloride.[124] This was followed by addition of aqueous hydrochloric acid to cleave the silyl ether and form alcohol **222** (Scheme 60). Under these conditions, the product **222** was formed in 31% isolated yield. Efforts were made to improve the outcome of this reaction, by increasing the equivalents of the reagents or changing the base to LDA or NaHMDS. However, all attempts ended with no reaction or forming a mixture of the product, the di-silylated intermediate and starting material. To improve the yield of this reaction, it would be better to initially protect the alcohol and then attach the silyl group.



168 **222**

Scheme 60: Formation of pent-4-yn-1-ol bearing a C-5 TBDMS group.

Disubstituted alkyne **222** was then subjected to a one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction, again under mild Masamune-Roush conditions. This exclusively allowed the formation of the corresponding (*E*)-α,β-unsaturated ester **223** in 80% yield. Reduction of **223** with DIBAL-H gave the alkynylsilyl-derived allylic alcohol **224** in 92% yield (Scheme 61).

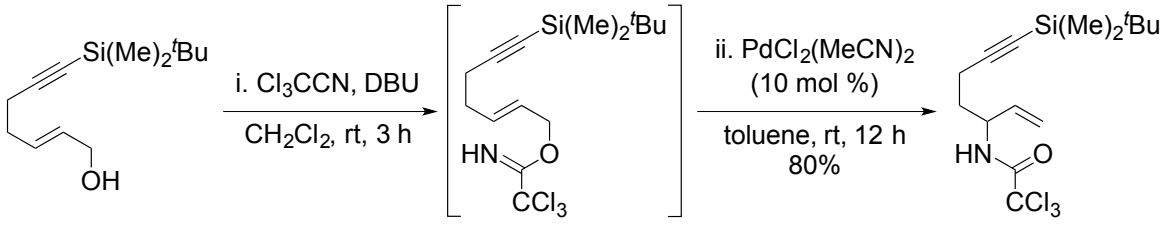


222 **223** **224**

Scheme 61: Synthesis of allylic alcohol 224.

2.2.2.2 One-pot palladium(II)-catalysed Overman rearrangement

Before attempting the one-pot process, each stage was investigated separately. Starting with the Overman rearrangement, allylic alcohol **224** was reacted with trichloroacetonitrile and a catalytic amount of DBU to form the corresponding allylic trichloroacetimidate **225**. Without further purification, compound **225** was subjected to a Pd(II)-catalysed Overman rearrangement. This allowed the formation of allylic trichloroacetamide **226** in 80% yield (Scheme 62). This result supported the previous hypothesis that the steric bulk was responsible for preventing the coordination of the catalyst to the alkyne, and enabling the Pd(II)-catalysed Overman rearrangement to proceed.

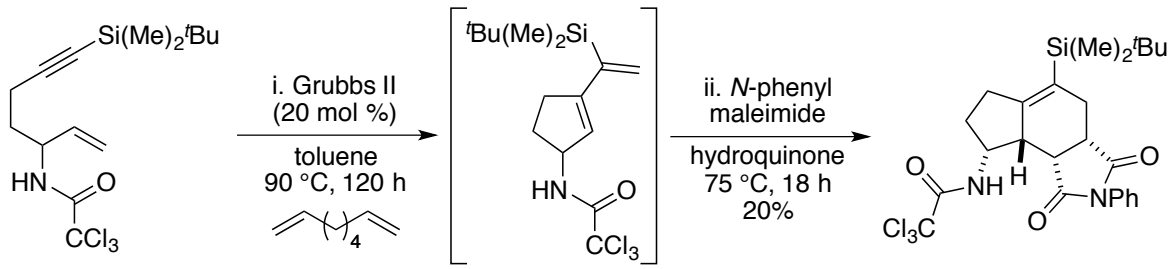


224 **225** **226**

Scheme 62: A one-pot Pd-catalysed Overman rearrangement.

2.2.2.3 One-pot RCEYM/Diels-Alder reaction

Attention was then turned to the RCEYM reaction of allylic trichloroacetamide **226**. The RCEYM reaction was carried out as previously described for similar substrates using Grubbs second-generation catalyst (10 mol %) and octa-1,7-diene at 90 °C (Scheme 63). Under these conditions, the reaction was slow and proceeded with poor conversion after 60 h. A second portion of Grubbs catalyst was added (10 mol %), and the reaction was left stirring at the same temperature for further 60 h. After consumption of all starting materials, *N*-phenylmaleimide and hydroquinone were added to the same pot, and the Diels-Alder reaction was completed in 18 h to give the desired TBDMS-derived aminobicyclo[4.3.0]nonane **227** as a single diastereomer in 20% yield over the one-pot, two-step process. The low yield was attributed to the ineffective RCEYM reaction, where the presence of the bulky TBDMS group obstructed the reaction of the alkyne, resulting in a slower reaction. The low yield may also due to decomposition of the formed diene at high temperature and long reaction time, which has been observed before with similar substrates.



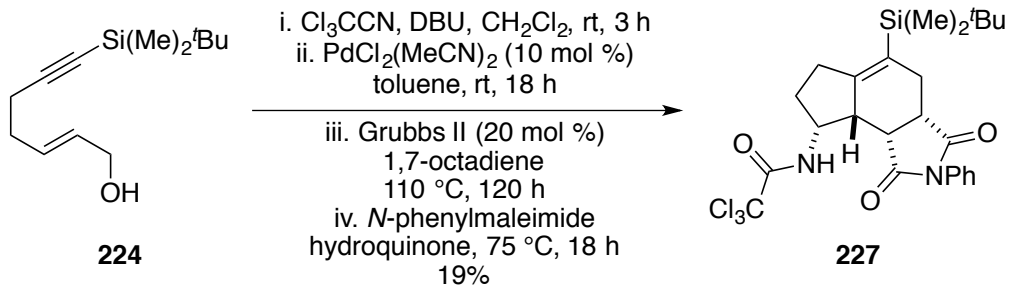
226 **227**

Scheme 63: One-pot RCEYM/Diels-Alder reaction of 226.

2.2.2.4 Attempted one-pot four-step synthesis of aminobicyclo[4.3.0]nonane 227

Allylic alcohol **224** was then subjected to the one-pot four-step process, using more forcing conditions for the RCEYM step of 20 mol % catalyst loading and performing the reaction at 110 °C. This gave the TBDMS-derived aminobicyclo[4.3.0]nonane **227** in 19% yield over the four steps (Scheme 64).

The work shows that while the bulky TBDMS group was sufficient to prevent the catalyst binding to the alkyne and enable the Pd(II)-catalysed Overman rearrangement, it had a detrimental effect on the following RCEYM reaction.

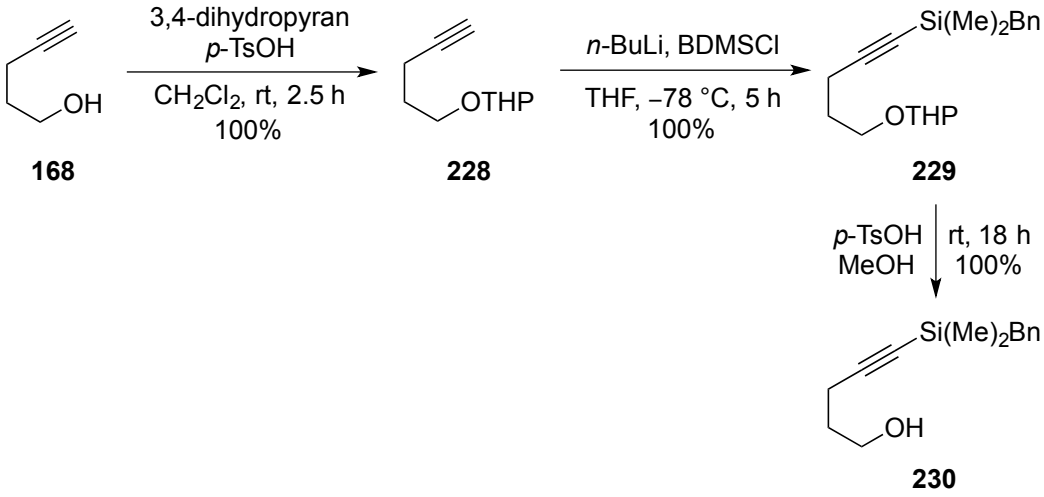


Scheme 64: Synthesis of 227 *via* one-pot multi-reaction process.

2.2.3 Development of a one-pot process using a benzyldimethylsilylalkynyl-derived allylic alcohol

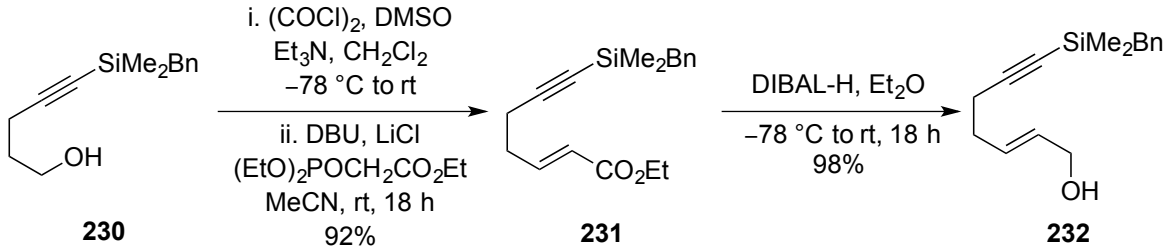
2.2.3.1 Synthesis of allylic alcohol

Having probed the steric requirements for the one-pot process, it was proposed that the less bulky BDMS group would allow a more efficient one-pot process. As usual, the synthetic route started with the preparation of the required allylic alcohol. To avoid any issues of side-reactions during the silylation step, the incorporation of the BDMS group was carried out stepwise. The hydroxyl group of pent-4-yn-1-ol (**168**) was first protected as a THP ether, giving 1-(tetrahydropyran-2-yloxy)-4-pentyne (**228**) in quantitative yield (Scheme 65). Compound **228** was then silylated with benzyldimethylsilyl chloride to give **229**. Finally, THP deprotection of **229** with *p*-toluenesulfonic acid in methanol gave 5-(benzyldimethylsilyl)pent-4-yn-1-ol (**230**) in quantitative yield.[125]



Scheme 65: Formation of BDMS-analogue 230.

The BDMS-derived disubstituted alkyne **230** was then subjected to a one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction under Masamune–Roush conditions, allowing the formation of the (*E*)-α,β-unsaturated ester **231** in 92% yield. Reduction of the ester **231** with DIBAL-H gave desired allylic alcohol **232** in 98% yield (Scheme 66).

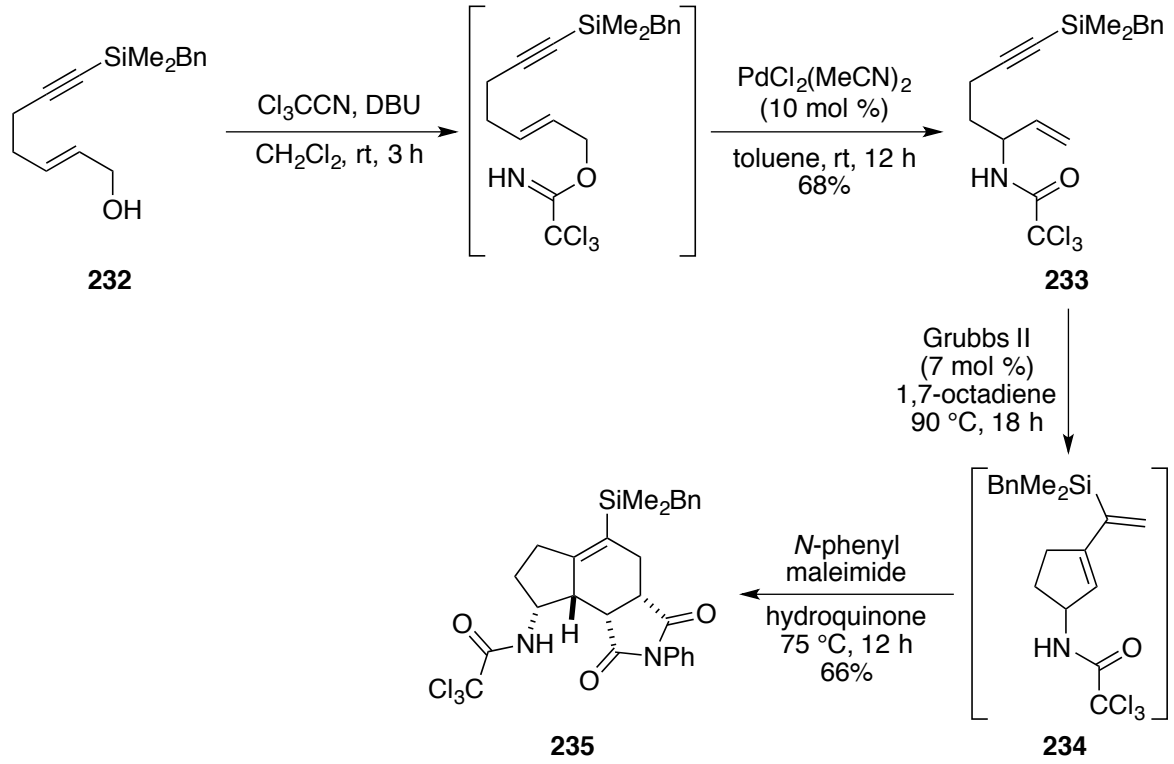


Scheme 66: Synthesis of allylic alcohol 232.

2.2.3.2 One-pot multi-step synthesis of aminobicyclo[4.3.0]nonane 235

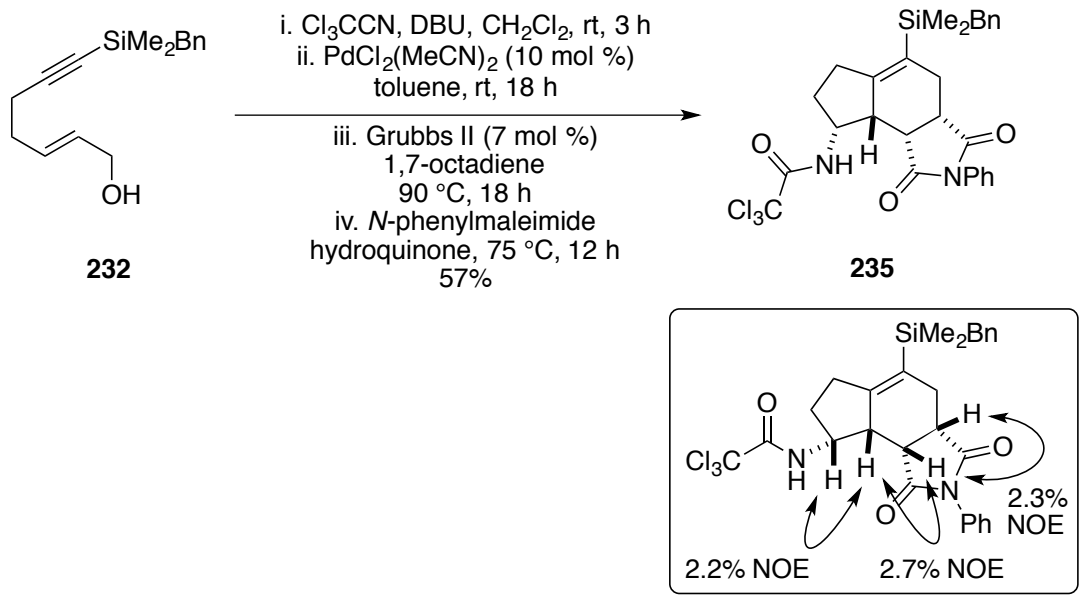
With allylic alcohol **232** in hand, the one-pot Pd-catalysed Overman rearrangement was first attempted. Under standard conditions, allylic trichloroacetamide **233** was successfully formed in 68% yield (Scheme 67). Allylic trichloroacetamide **233** was then subjected to a RCEYM reaction in the presence of Grubbs second generation catalyst (7 mol %) and octa-1,7-diene at 90 °C. As expected, the ^{1}H NMR spectrum of the crude RCEYM reaction showed the clean conversion of allylic trichloroacetamide **233** to the diene **234** after 18 hours. *N*-Phenylmaleimide as a dienophile was then added and the final BDMS-derived aminobicyclo[4.3.0]nonane

235 was isolated as a single diastereomer in 66% yield.



Scheme 67: Two-pot synthesis of aminobicyclo[4.3.0]nonane 235.

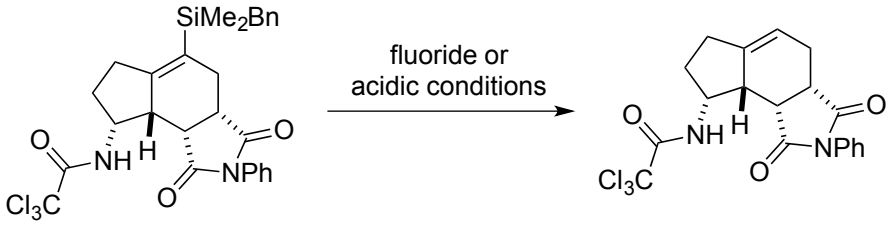
Starting from allylic alcohol **232**, the one-pot four-step process involving Pd(II)-catalysed Overman rearrangement, RCEYM and Diels-Alder reaction was then performed. This gave final product **235** in 57% overall yield (Scheme 68). The relative stereochemistry of diastereomer **235** was confirmed by NOE experiments which showed the *syn*-relationship of the hydrogen atoms at C-3a, C-8, C-8a and C-8b.



Scheme 68: One-pot four-step synthesis of aminobicyclo[4.3.0]nonane 235.

2.2.4 Protodesilylation reaction

Having identified a suitable silane for the one-pot process and successfully prepared the desired vinylsilyl derived aminobicyclo[4.3.0]nonane **235**, attention then turned to using this vinylsilane for a late stage synthesis of various derivatives. Initially, removal of the BDMS group to form the non-substituted analogue was investigated. Under standard fluoride conditions, treatment of vinylsilane **235** with TBAF at room temperature showed no reaction (Table 7, entry 1). Using more forcing conditions by increasing the temperature (up to 60 °C) and the reaction time (24 h) only led to decomposition with no starting materials or product recovered (entry 2). Alternatively, attempts were made to cleave the C−Si bond under acidic conditions. Starting with 2 M hydrochloric acid and methanol (1:1 ratio), there was no reaction at room temperature after 24 h (entry 3). Using a more concentrated acid (4 M HCl) and by performing the reaction at 45 °C, a 42% conversion to **236** was observed after 48 h (entry 4). Finally, the synthesis of the non-substituted aminobicyclo[4.3.0]nonane **236** was achieved in 74% yield using 6 M HCl at 60 °C (entry 5). These results showed that the BDMS group is stable to protodesilylation under fluoride and mild acidic conditions.



235 **236**

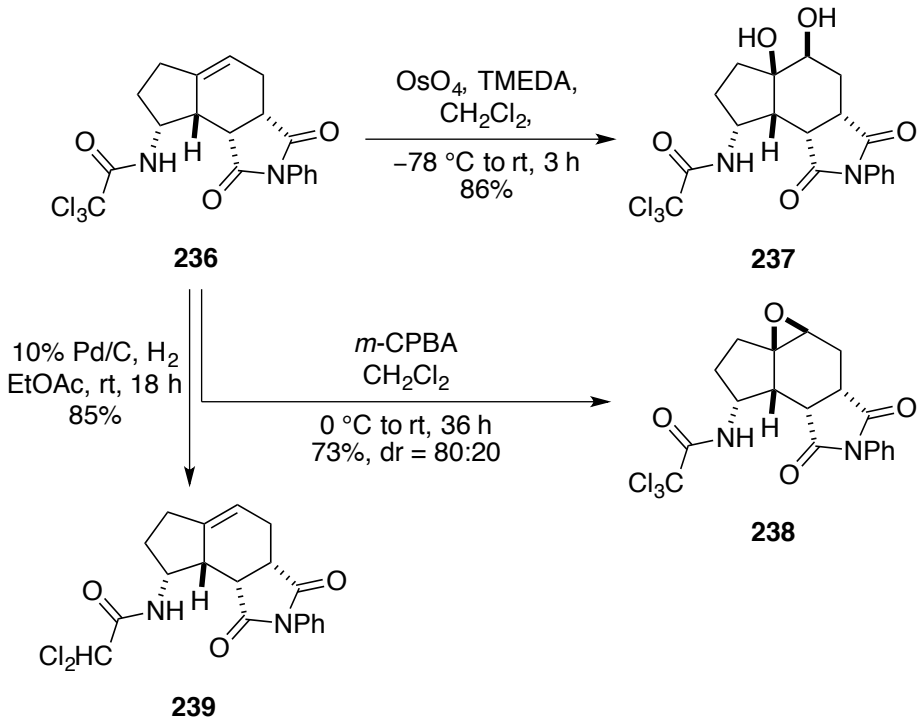
Entry	Reagent	Conditions	Conversion (%)	Yield (%)
1	TBAF, THF	20 °C, 6 h	No reaction	-
2	TBAF, THF	60 °C, 24 h	Decomposition	-
3	2 M HCl, MeOH (1:1), THF	20 °C, 24 h	No reaction	-
4	4 M HCl, MeOH (1:1), THF	45 °C, 48 h	42	-
5	6 M HCl, MeOH (1:1), THF	60 °C, 18 h	100	74

Table 7: Protodesilylation reaction to form non-substituted analogue 236.

2.2.4.1 Functionalisation of aminobicyclo[4.3.0]nonane 236

The next stage of this project was to investigate the reactivity of the tri-substituted alkene component of compound **236** toward oxidation reactions. Firstly, under Donohoe's conditions using osmium tetroxide and TMEDA,[116,117] dihydroxylation of **236** gave the desired diol derivative **237** in 86% yield as a single diastereomer (Scheme 69). Similarly, an epoxidation reaction of **236** with *m*-CPBA was carried out and gave epoxide **238** as a major diastereomer in 73% yield. Diol derivative **237** was formed as a single diastereomer in contrast to the epoxidation reaction that gave **238** as a major diastereomer in a 5:1 ratio. Due to the small-scale reaction, the minor epoxide diastereomer was difficult to isolate after column chromatography. The selectivity observed for these reactions was due to the curved shape of the tricyclic core of **236**, which allowed the reactions to take place on the less hindered top face of the molecule. The facial selectivity of these type of reactions with aminobicyclo[4.3.0]nonanes such as **237** has been confirmed by the X-ray crystal structure of a similar molecule **216** (see figure 8, section 2.1.6). Finally, attempts were made to reduce the alkene of bicyclo[4.3.0]nonane **236** using 10% palladium on carbon under an atmosphere of hydrogen. The alkene

was resistant to hydrogenation and the reaction produced only dichloroacetamide analogue **239** in 85% yield.



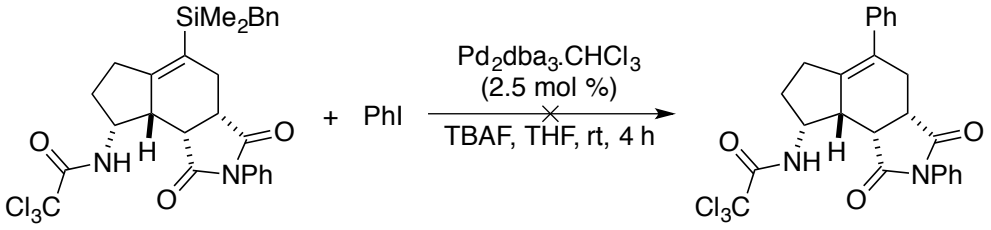
Scheme 69: Functionalisation of the tri-substituted alkene of compound 236.

2.2.5 Attempted Hiyama-Denmark cross coupling

One of the main aims of this project was to enable the palladium catalysis of the Overman rearrangement to take place during the one-pot process. Therefore, the asymmetric synthesis of this aminobicyclo[4.3.0]nonane core could be achieved using chiral palladium catalysts such as (*S*)-COP-Cl **56** and (*R*)-COP-Cl **57**. The previous study showed that the use of disubstituted alkynes with an aryl group attached was necessary to hinder the coordination of the palladium catalyst to the alkyne side-chain and facilitate the Pd(II)-catalysed Overman rearrangement. This allowed the formation of a library of aminobicyclo[4.3.0]nonanes **201**–**213** diastereoselectively in good overall yields. However, there were only two ways to introduce the diversity of this process, either *via* a Sonogashira cross coupling before the synthesis of the allylic alcohol precursors or a Diels-Alder reaction at the final stage of this process using different dienophiles. To overcome this limitation, another one-pot process using BDMS-derived allylic alcohol was developed and successfully led to the synthesis of vinylsilyl derived

aminobicyclo[4.3.0]nonane **235** in a good yield. The use of the vinylsilane functionality in cross coupling reactions was then investigated to allow the late-stage diversification to various aminobicyclo[4.3.0]nonanes.

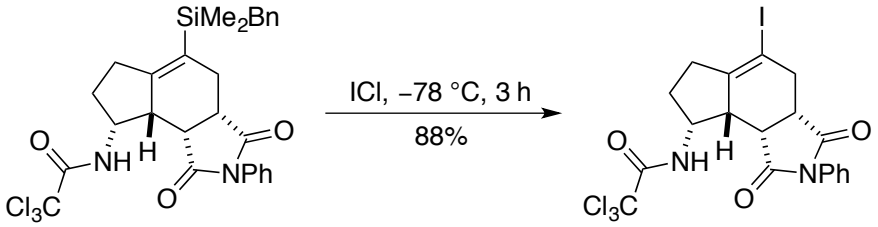
Under standard conditions, a Hiyama-Denmark reaction was attempted to couple the vinylsilyl derived aminobicyclo[4.3.0]nonane **235** with iodobenzene in the presence of tris(dibenzylideneacetone)dipalladium(0) (2.5 mol %) and TBAF (Scheme 70).[122] However, all attempts failed and neither product nor starting material was recovered. Other conditions, such as increasing the catalyst loading (up to 10 mol %) and the temperature (40, 60 and 80 °C), or using electron rich (4-iodoanisole) and electron poor (1-iodo-4-nitrobenzene) coupling partners were investigated, but all efforts ended with decomposition of vinylsilane **235**.



Scheme 70: Attempted Hiyama-Denmark cross coupling reaction of 235.

2.2.6 Iododesilylation reaction

In a similar fashion to the protodesilylation reaction and to overcome the issue with the Hiyama-Denmark reaction, it was found that the vinylsilane **235** could undergo an iododesilylation reaction to form the corresponding vinyl iodide **240**.[126,127] Using iodine monochloride at −78 °C, the vinylsilane **235** was transformed into the vinyl iodide **240** in a 88% yield (Scheme 71). The successful synthesis of vinyl iodide **240** was promising, as this could be used to explore other palladium-catalysed cross-coupling reactions such as Suzuki and Sonogashira reactions.

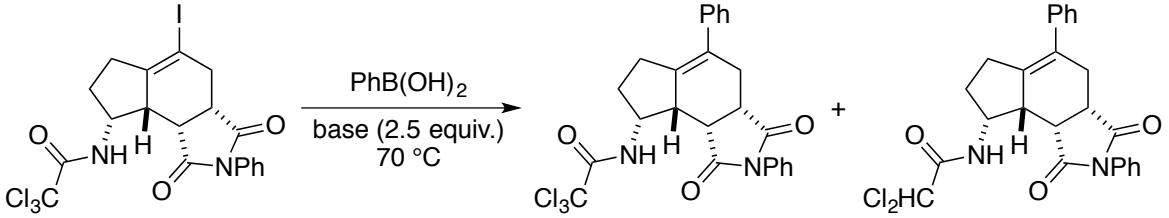


Scheme 71: Synthesis of vinyl iodide 240 *via* iododesilylation reaction.

2.2.6.1 Suzuki cross-coupling reaction

Following the issues encountered with the Hiyama-Denmark coupling, the first suggestion was to attempt a Suzuki coupling reaction using vinyl iodide **240**. Initially, compound **240** was subjected to a Suzuki coupling reaction with phenylboronic acid in the presence of [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (5 mol %) and cesium fluoride (Table 8, entry 1). With these conditions, the reaction proceeded with low conversion and gave the product **201** along with the dechlorinated compound **214** as a by-product in a 4:1 ratio, respectively. Changing the base to cesium carbonate gave a better conversion, but again produced by-product **214** (entry 2). Using bis(triphenylphosphine)palladium(II) dichloride as a catalyst and shorter reaction times, with different catalyst loading gave coupled product **201** and compound **214** in low yield (entries 3, 4 and 5). Decomposition was observed when tetrakis(triphenylphosphine)palladium(0) was used as the catalyst with cesium fluoride or potassium carbonate as bases in 1,4-dioxane or DMF (entries 6 and 7). Fortunately, when the solvent system was changed to toluene and methanol with potassium carbonate as a base and $Pd(PPh_3)_4$ as the catalyst, a high yield was obtained for both compounds with the ratio of 1:2 of the target product **201** and the by-product **214**, respectively (entry 8). Monitoring the reaction progress by ^1H NMR spectroscopy showed that the dechlorination happened immediately after the formation of the product **201**. To increase the reaction rate, a higher catalyst loading of 10 mol% was trialed, hoping that the target product **201** would be formed quickly before the dechlorination started. This led to the formation of compound **201** in a better ratio (2:1) (entry 9). Finally, using increased equivalents of base (4 equiv.) and 10 mol% of the catalyst gave the cross-coupled

product **201** in 76% yield as a major product (entry 10). During the optimisation of this reaction, it was thought that the problem could be associated with the palladium catalyst. Therefore, further investigation was carried out using other transition metal catalysts, such as (1,3-bis(diphenylphosphino)propane)nickel(II) dichloride. However, this led to no reaction.

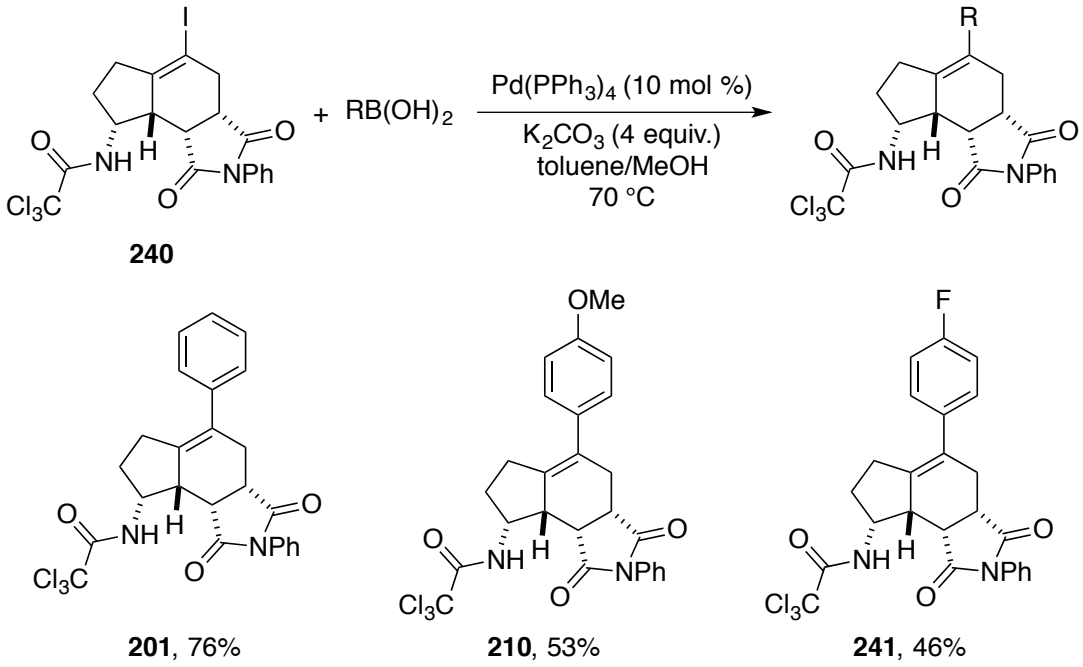


240 **201** **214**

Entry	Catalyst (mol %)	Base, Solvent, Time	Conversion (%)[a] Ratio (**201**:**214**:**240**)	Yield (%)[b] **201**:**214**
1	$PdCl_2$(dppf) (5)	CsF, 1,4-dioxane, 24 h	22 (4:1:13)	-
2	$PdCl_2$(dppf) (5)	$CsCO_3$, 1,4-dioxane/H_2O, 24 h	69 (2.4:1:2)	-
3	$PdCl_2(PPh_3)_2$ (5)	K_2CO_3, 1,4-dioxane/H_2O, 4 h	100 (2:1:0)	32:15
4	$PdCl_2(PPh_3)_2$ (2.5)	K_2CO_3, 1,4-dioxane/H_2O, 7 h	88 (4.2:2:1)	20:10
5	$PdCl_2(PPh_3)_2$ (10)	K_2CO_3, 1,4-dioxane/H_2O, 3 h	87 (4:1.7:1)	-
6	$Pd(PPh_3)_4$ (5)	CsF, 1,4-dioxane, 5 h	Decomposition	
7	$Pd(PPh_3)_4$ (5)	K_2CO_3, DMF/H_2O 18 h	Decomposition	
8	$Pd(PPh_3)_4$ (5)	K_2CO_3, toluene/MeOH 48 h	100 (1:2:0)	32:53
9	$Pd(PPh_3)_4$ (10)	K_2CO_3, toluene/MeOH 48 h	100 (2:1:0)	-
10[c]	$Pd(PPh_3)_4$ (10)	K_2CO_3, toluene/MeOH 48 h	92	76:5

Table 8: Optimisation of Suzuki coupling reaction. [a]Calculated from ^{1}H NMR spectra of crude reaction mixture, [b]Isolated yield after purification. [c]The reaction was performed using four equivalents of K_2CO_3.

Having established the required conditions for the Suzuki coupling to form **201** using phenylboronic acid as a coupling partner, attention was then turned to electron-rich and electron-deficient variants (Scheme 72). Under the optimised conditions, reaction of vinyl iodide **240** with 4-methoxyphenylboronic acid gave the corresponding coupled product **210** in a 53% yield. As observed during the synthesis of **201**, small amounts of the dichloroacetamide analogue **210b** were detected (10%). The mono-dechlorinated product was still observed in high amounts during the reaction of compound **240** with electron-deficient 4-fluorophenylboronic acid. However, the formation of this by-product was reduced to less than 10% by using a shorter reaction time. This allowed the synthesis of the aminobicyclo[4.3.0]nonane analogue **241** in a 46% yield in 12 h.

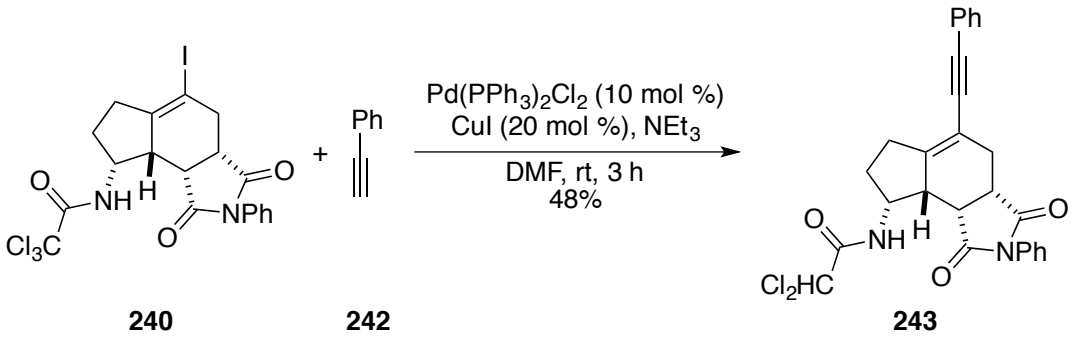


Scheme 72: Suzuki cross-coupling reaction of 240 with electron electron-rich and electron-deficient coupling partners.

2.2.6.2 Sonogashira cross-coupling reaction

The late-stage diversity of aminobicyclo[4.3.0]nonanes was further expanded with the coupling of other groups at the C-5 position *via* a Sonogashira reaction. This work was carried out by Angus McMillan, a project student in the group. Under standard conditions, the reaction was performed using phenylacetylene **242** as a coupling partner in the presence of bis(triphenylphosphine)palladium dichloride (1

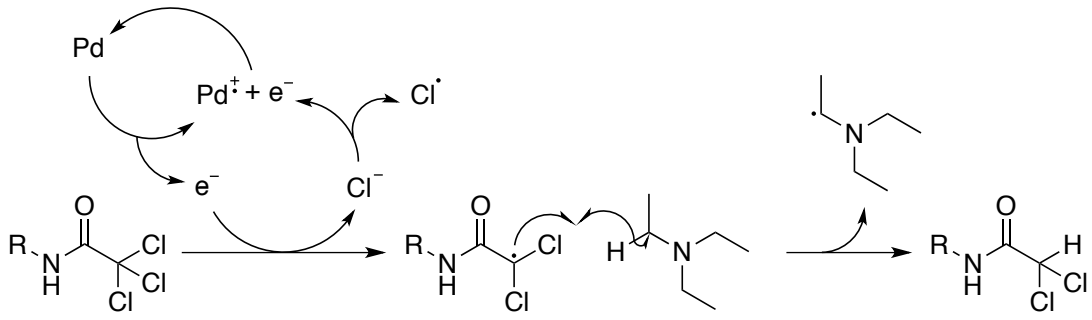
mol %) and copper iodide (2 mol %) in triethylamine and DMF as a co-solvent (Scheme 73).[128] This gave a mixture of dechlorinated starting material and couple of different unidentified by-products. Increasing the catalyst loading to 10 and 20 mol % of the palladium and copper catalysts allowed the synthesis of the dechlorinated C-5 substituted product **243** in a 48% yield. It should be mentioned that after two hours, the ^{1}H NMR spectra of the crude reaction mixture showed the consumption of all starting material **240** and the formation of a mixture of both the expected coupled product and the mono-dechlorinated product **243**. Because of the rapid transformation to both products, the reaction was left stirring for an additional hour to exclusively form compound **243**. This was the best result obtained from different attempts using various catalysts and bases.



240 **242** **243**

Scheme 73: Sonogashira cross-coupling reaction of 240.

The proposed mechanism for the formation of dichloroacetamide **243** is shown in Scheme 74. It was believed that the dechlorination occurred *via* a single electron transfer (SET) mechanism similar to what has been previously observed for platinum-catalysed dechlorination of the trichloromethylcarbonyl group.[129] This observation was supported by Liu, Dong and co-workers who described a similar SET mechanism for palladium catalysts.[130]



Scheme 74: Proposed dechlorination mechanism.

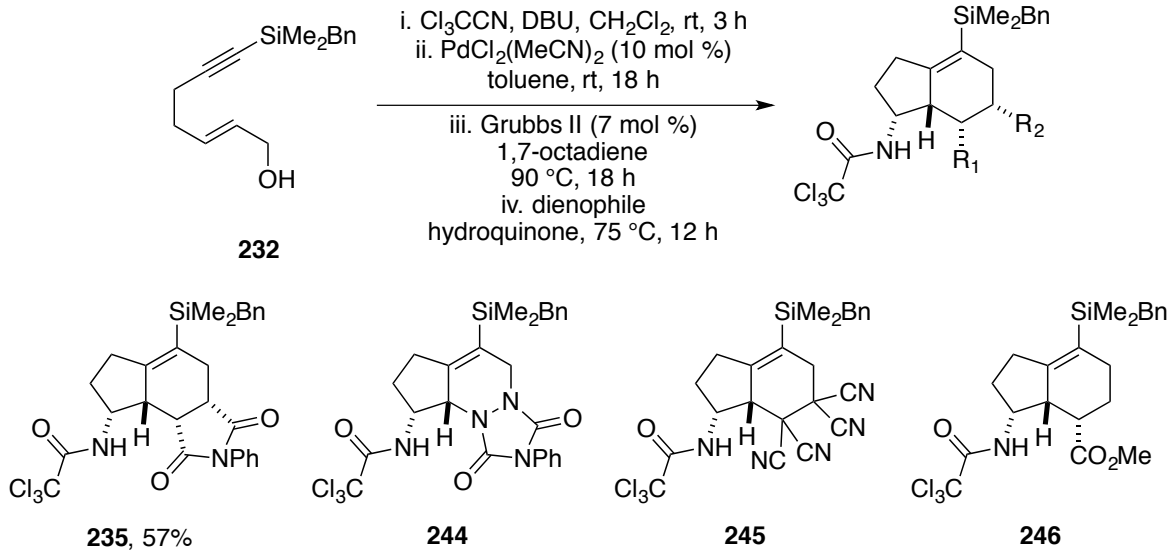
2.2.7 Conclusions

In conclusion, two silyl substituted hep-2-en-6-yn-ols have been prepared and examined as substrates for the one-pot multi-step synthesis of novel vinylsilyl derived aminobicyclo[4.3.0]nonanes. Initially, a TBDMS group was used to investigate the steric requirements for the one-pot process. It was found that while the presence of this group was effective to perform the Pd-catalysed Overman rearrangement, it hindered the following RCEYM reaction. Alternatively, the less bulky BDMS group was then examined and successfully led to the formation of the corresponding aminobicyclo[4.3.0]nonane **235** in a good yield over the four-step process. The resulting vinylsilane **235** was then submitted to protodesilylation and iododesilylation reactions leading to the synthesis of the non-substituted **236** and vinyl iodide **240** derivatives. Next, the reactivity of compounds **236** and **240** towards oxidation and cross-coupling reactions was investigated and led to the late stage synthesis of various sp^3-rich aminobicyclo[4.3.0]nonanes.

2.2.8 Future work

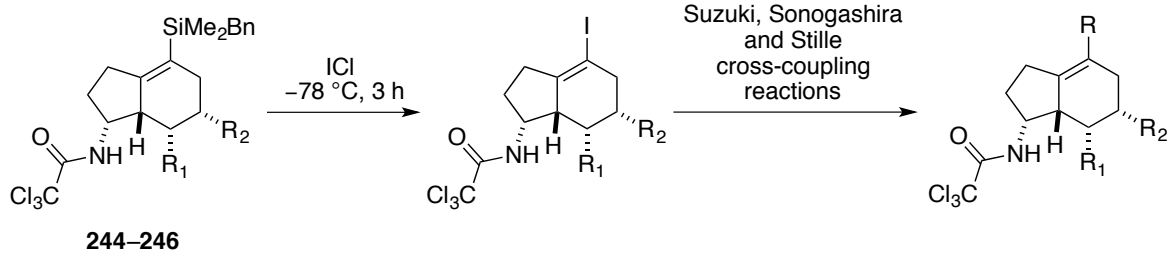
During this course of study, a one-pot four-step process was successfully developed for the diastereoselective synthesis of a novel BDMS-derived aminobicyclo[4.3.0]nonane **235** in a good overall yield. This one-pot process involved a Pd(II)-catalysed Overman rearrangement, Ru(II)-catalysed RCEYM and hydrogen bonding Diels-Alder reactions. To examine the requirements for the one-pot process, this work focused only on using *N*-phenylmaleimide as a dienophile for the Diels-Alder reaction. Exploring the scope of dienophile during the Diels-Alder reaction will be the next stage of this project (Scheme 75). This could be

achieved by using different dienophiles such as 4-phenyl-1,2,4-triazole-3,5-dione, tetracyanoethylene and methyl acrylate during the final step.



Scheme 75: Exploring the scope of the process using different dienophiles.

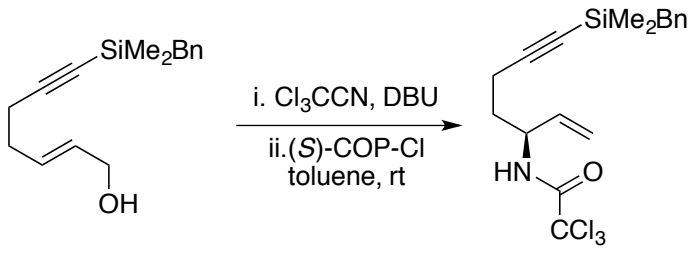
Having successfully synthesised the vinylsilyl derivatives **244**–**246**, these would be then undergo iododesilylation reactions to form the corresponding vinyl iodide. By utilising these vinyl iodides in different cross coupling reactions, such as Suzuki, Sonogashira and Stille reactions, the scope of this study would be further expanded for the late-stage generation of a large library of analogues (Scheme 76).



Scheme 76: Exploring the scope of the process using different dienophiles.

After the successful development of the one-pot multi-reaction process involving a Pd(II)-catalysed Overman rearrangement for the diastereoselective synthesis of various aminobicyclo[4.3.0]nonanes, the final stage of this project will be the asymmetric synthesis of these compounds. This could be achieved by using a

chiral palladium catalyst such as (*S*)-COP-Cl **56** during the Overman rearrangement step (Scheme 77). Once the reaction has been fully optimised, this will be then utilised in a one-pot process including RCEYM and Diels-Alder reactions to synthesise the corresponding chiral vinylsilyl.



Scheme 77: Proposed asymmetric Overman rearrangement using chiral catalyst.

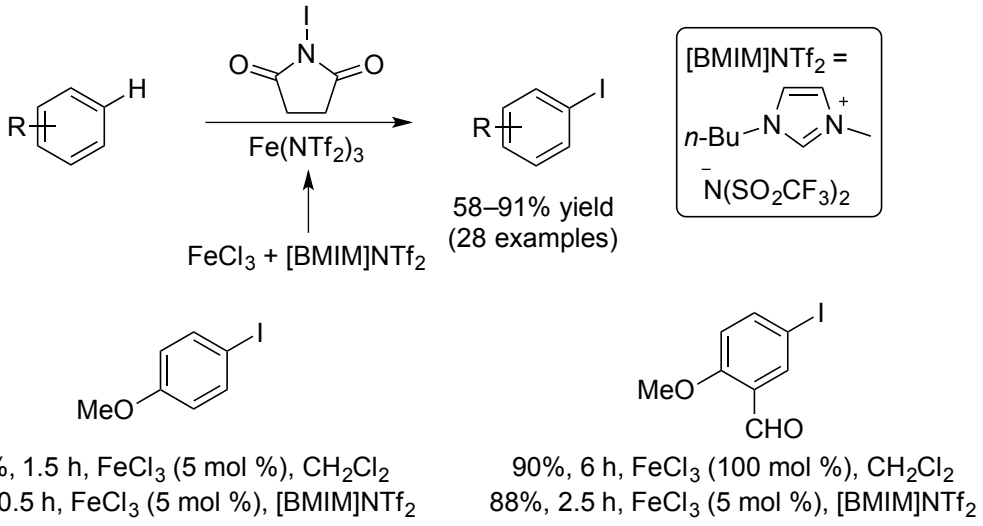
2.3 Development of a one-pot two-step procedure for aryl C-H amination using iron and copper catalysis

2.3.1 Introduction and previous work within the Sutherland group

Aryl halides are highly useful synthetic intermediates in organic synthesis, used in several synthetic transformations, such as the construction of C–C, C–N, C–O and C–S bonds *via* Pd-, Ni- and Cu-catalysed cross coupling reactions, the formation of organometallic reagents and also as precursors for nucleophilic aromatic substitution reactions.[131−133] These compounds also have great importance in medicinal chemistry, because of their applications in understanding diseases with the use of aryl compounds containing radioactive halogen isotopes.[134,135] Generally, aryl iodides and bromides have better reactivity than aryl chlorides and fluorides, and can be used in different chemical reactions, because of their weaker C-X bonds. Several methods have been developed for preparing this important class of compounds. These include metal-catalysed halogen exchange, the Sandmeyer reaction and most commonly, electrophilic aromatic halogenation.[136−140] However, most of these methods require the use of expensive and toxic transition metals, harsh conditions and sometimes give products with poor regioselectivity.

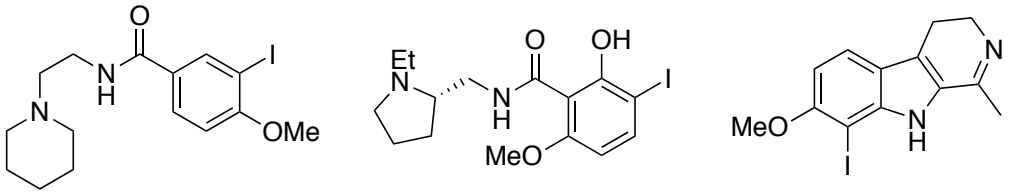
In order to develop an alternative cost-efficient catalytic method, Racys and Sutherland have developed an important and highly regioselective iodination method of activated arenes *via* iron(III)-catalysed activation of *N*-iodosuccinimide (NIS).[141a] This work investigated a general aryl iodination method using iron(III) triflimide, which is a strong Lewis acid generated *in situ* from the reaction of iron(III) chloride and triflimide-based ionic liquid, 1-butyl-3-methyl-imidazolium bis(trifluoromethylsulfonyl)imide ([BMIM]NTf_2). The use of the inexpensive, non-pollutant and non-toxic iron(III) chloride catalyst and a cheap and recyclable ionic liquid have made this method very efficient, enabling rapid reactions to proceed under mild conditions using low catalyst loading. It was clearly noticed that the ionic character of the ionic liquid produces high cohesive pressure,[141b] which increased the reaction rate, in particular with substrates containing strong deactivating groups.

For example, the iodination of substrates such as anisole with $FeCl_3$ (5 mol %) and NIS in dichloromethane as a solvent gave 4-iodoanisole in a 86% yield in 1.5 h (Scheme 78).[141a] On the other hand, when [BMIM]NTf_2 was used as a solvent, 89% yield was achieved in 0.5 h. In comparison, with less reactive substrates such as 2-methoxybenzaldehyde, it was found that a higher catalyst loading (100 mol %) of $FeCl_3$ was required to give 90% of 2-methoxy-5-iodobenzaldehyde in 6 h, when the reaction was performed in dichloromethane. Alternatively, the use of a catalytic amount of $FeCl_3$ (5 mol %) in ionic liquid gave 2-methoxy-5-iodobenzaldehyde in 88% yield and a decreased reaction time of 2.5 h. Therefore, in this process, the ionic liquid was used as a solvent and as a source of triflimide to activate the iron catalyst. The process was then applied to a wide range of substrates tolerating different activating and deactivating groups, resulting in the formation of a library of iodinated arenes in high yields under mild conditions and short reaction times. During this work, it was also shown that the iodination proceeds *via* a two-electron transfer mechanism, and this was proven by adding the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), which had no effect on the reaction outcome. It is believed that higher *para* selectivity is due to the greater frontier orbital coefficient for the HOMO of the *para* position which is estimated to be 0.47 compared to 0.31 for the HOMO of the *ortho* position.[141c] This was shown by Leblanc and Boudreault for the amination of anisole.[141d] The regiochemistry observed for this reaction is similar to that seen in other halogenation reactions of activated aryl compounds.[141e–g]



Scheme 78: Iron triflimide catalysed iodination of activated arenes.

The process was successfully used to synthesise important medicinal compounds. For example, the preparation of PIMBA (**247**) which is a compound used for imaging breast tumors,[142] was achieved in 84% yield (Figure 9). Other targets such as (–)-IBZM (**248**), a SPECT imaging agent and a human D_2 receptor,[143] and 8-iodoharmaline (**249**), a monoamine oxidase inhibitor,[144] were synthesised in 47% and 73% yield, respectively.[141a]



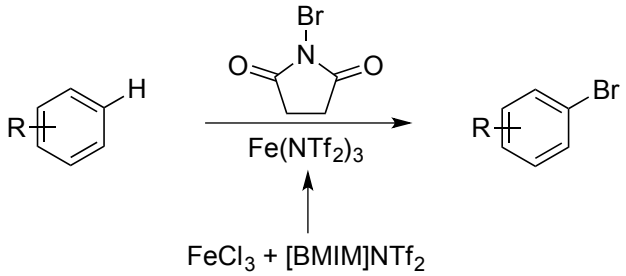
PIMBA (**247**), 84% (–)-IBZM (**248**), 47% 8-iodoharmaline (**249**), 73%

Figure 9: Examples of medicinal compounds prepared by iron triflimide catalysed iodination.

2.3.2 Bromination of arenes using iron(III) triflimide

2.3.2.1 Aims

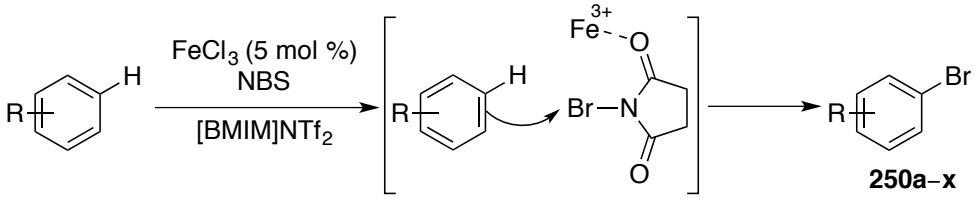
The first aim of this project was to investigate the iron(III)-catalysed bromination of activated arenes using *N*-bromosuccinimide (NBS) as the brominating reagent in the triflimide based ionic liquid, [BMIM]NTf_2 (Scheme 79).[145]

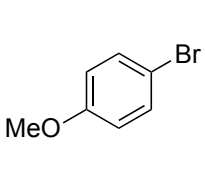


Scheme 79: Iron triflimide catalysed bromination of activated arenes.

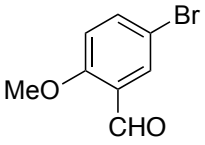
2.3.2.2 Substrate scope

Using a similar procedure to that described in Scheme 78, the scope of the iron(III) triflimide activation of *N*-bromosuccinimide (NBS) was evaluated. This transformation was found to be applicable to a wide range of anisole, aniline and alcohol derivatives (Scheme 80). Bromination of substrates with electron donating group such as anisole gave 4-bromoanisole (**250a**) in excellent yield with a 95:5 ratio of *p*- and *o*-isomers. Apart from anisole, all other aryl bromides were generated as single monobrominated regioisomers. Arenes with strong deactivating groups attached were also tested. For example, 4-nitroaniline was brominated in 2 h, and gave product **250n** in 80% yield. Substrates with a carboxyl group such as 4-methoxybenzoic acid and 2,4-dimethoxybenzoic acid were also examined and gave products **250e** and **250f** in 83% and 65% yields, respectively. The bromination process was also applied to highly active phenol substrates such as phenol, 2-fluorophenol, 2,4-dimethoxy-6-hydroxybenzaldehyde and 2-naphthol, affording the corresponding brominated products (**250i**–**k** and **250v**) in high yields. The scope of the process was further explored to include other active substrates such as 1-methoxynaphthalene, 2-methoxynaphthalene and 2,3-dihydrobenzofuran, giving the corresponding products **250t**, **250u**, and **250w** in excellent yields. From this study, it was found that the bromination using this method was more efficient than iodination, in terms of reaction times and isolated yields. The iron(III)-catalysed bromination method was also used to prepare 3,5-dibromo-4-hydroxybenzonitrile (bromoxynil) (**250x**), which is a mass produced herbicide, used to control weeds in corn, cereals and other vegetables.[146] The synthesis of **250x** was achieved in 91% yield from the reaction of 4-cyanophenol with 2 equivalent of NBS in 2.5 h.

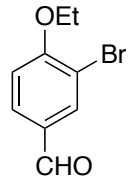




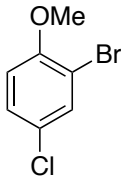
250a, 82%[a]
40 °C, 1.5 h



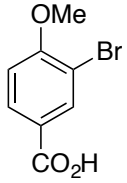
250b, 88%
40 °C, 1.5 h



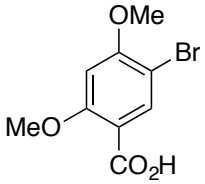
250c, 88%
40 °C, 22 h



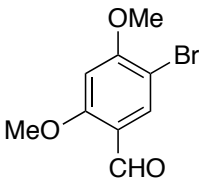
250d, 99%
40 °C, 1 h



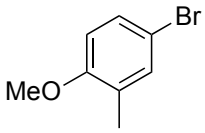
250e, 83%
40 °C, 4 h



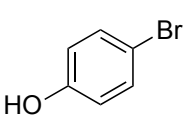
250f, 65%
40 °C, 4 h



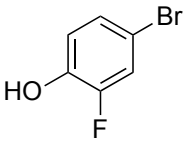
250g, 94%
20 °C, 2.5 h



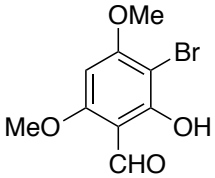
250h, 90%
40 °C, 2 h



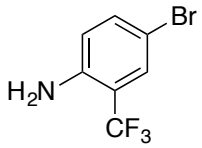
250i, 93%
20 °C, 0.5 h



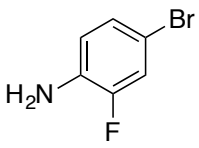
250j, 82%
40 °C, 2 h



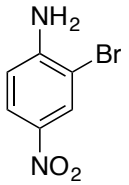
250k, 74%
20 °C, 6 h



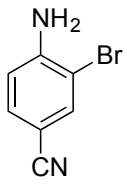
250l, 99%
40 °C, 2 h



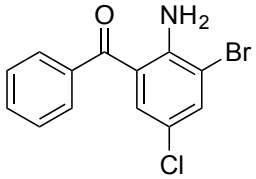
250m, 73%
20 °C, 1.5 h



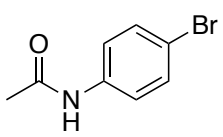
250n, 80%
40 °C, 2 h



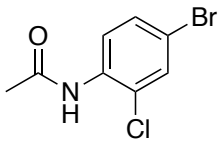
250o, 59%
40 °C, 22 h



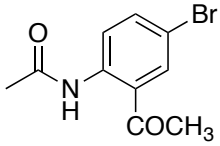
250p, 90%
70 °C, 1 h



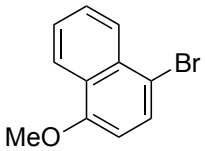
250q, 96%
40 °C, 2.5 h



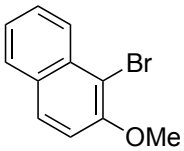
250r, 98%
40 °C, 3 h



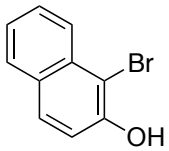
250s, 99%
40 °C, 3.5 h



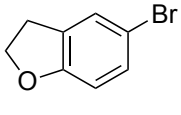
250t, 89%
40 °C, 2 h



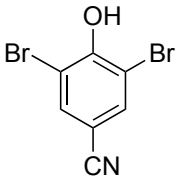
250u, 93%
40 °C, 2 h



250v, 90%
40 °C, 1 h



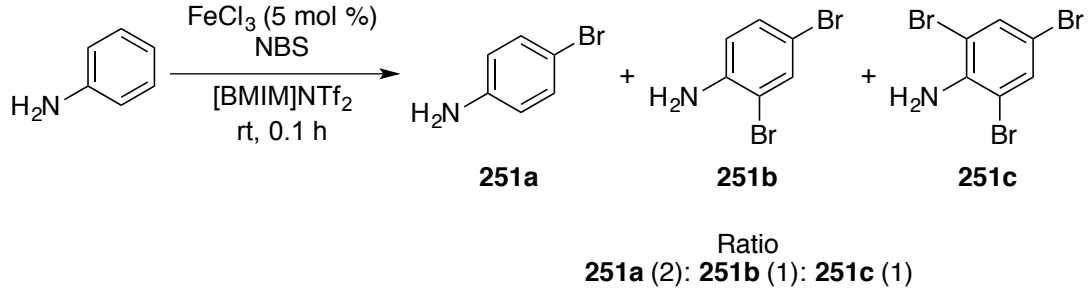
250w, 98%
40 °C, 1 h



250x, 91%
40 °C, 2.5 h

Scheme 80: Scope of iron triflimide catalysed bromination process. [a]A 95:5 ratio of *p*- and *o*-isomers.

The only limitation observed with this iron(III) catalysed method was the bromination of aniline which gave a mixture of the mono-, di- and tri-brominated anilines **251a**–**251c** in a 2:1:1 ratio (Scheme 81). The bromination was found to be very rapid at room temperature. In an attempt to slow the reaction, the temperature was lowered to 0 °C or –10 °C. However, this gave the same mixture of compounds.



Scheme 81: Attempted bromination of aniline.

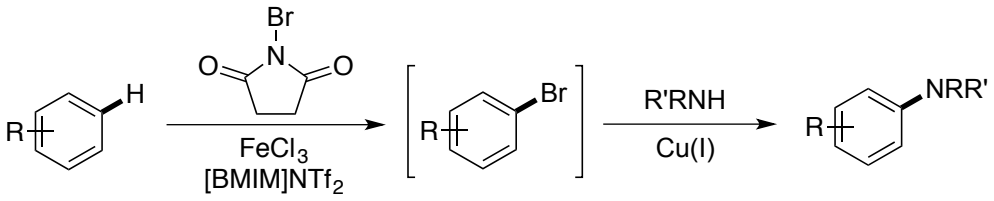
2.3.3 One-pot iron-catalysed bromination and copper(I)-catalysed *N*-arylation of aromatic compounds

2.3.3.1 Introduction and aims

The formation of aryl C–N bonds is of great importance in medicinal chemistry and natural product synthesis.[147–149] Various metal-catalysed methods have been developed for the selective synthesis of this valuable motif. These include the use of copper- (Ullman-Goldberg and Cham-Lam coupling)[150–153] or palladium- (Buchwald-Hartwig coupling)[154–157] catalysed amination or amidation of aryl (pseudo)-halides. However, these methods require prefunctionalisation or preoxidation of either one of the cross-coupling partners. Recently, a new class of transition-metal-catalysed amination methods which involve C–H/N–H bond activation have been reported.[158–164] Significant progress has been made towards the metal-catalysed cross-dehydrogenative *ortho*-amination coupling for the direct formation of C–N bonds.[164] However, only few examples have been reported for *meta*- and *para*-amination processes.[165,166]

The aim of this project was to develop a one-pot, two-step method for amination of *para*-C–H bonds using a combination of iron(III)- and copper(I)-catalysis (Scheme

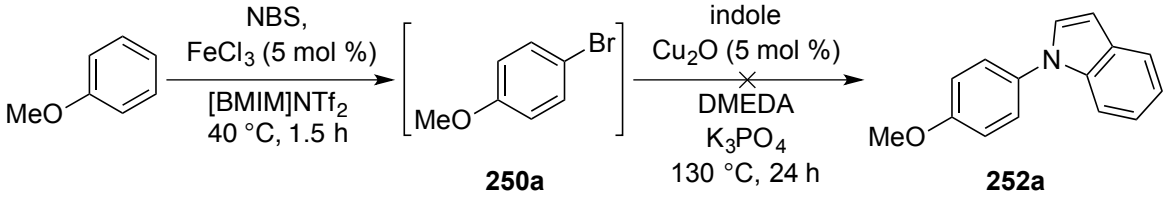
82). The one-pot process involves an iron(III)-catalysed bromination of activated arenes followed by a copper(I)-catalysed *N*-arylation reaction.



Scheme 82: One-pot *para*-C–H/N–H coupling using a combination of iron(III)- and copper(I)-catalysis.

2.3.3.2 Optimisation

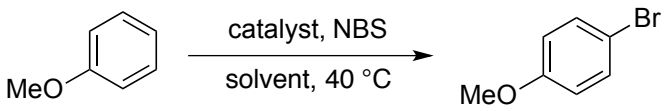
After identifying the optimal conditions for the bromination step, the next stage of this study was to include a copper(I)-catalysed *N*-arylation coupling. Anisole was chosen as a model substrate. The process started with the bromination of anisole with NBS in the presence of $FeCl_3$ (5 mol %) in $[BMIM]NTf_2$ as a solvent (Scheme 83). After completion of the first step, indole as a nucleophilic partner, copper(I) oxide, *N*,*N*'-dimethylethylenediamine as a ligand, and potassium phosphate were then added. Unfortunately, with these conditions, there was no reaction for the second step after stirring at 130 °C for 24 h. Changing the copper source to copper(I) iodide and the base to potassium carbonate or cesium carbonate gave the same result.



Scheme 83. First attempted one-pot process in $[BMIM]NTf_2$.

It was proposed that the problem of *N*-arylation reaction could be associated with using the ionic liquid as a solvent. This may be due to the triflimide ion acting as a ligand and coordinating to the copper centre, which prevented the catalyst ligation to the arene. To overcome this issue, the bromination step was further investigated using catalytic amounts of the ionic liquid and other solvents. As previously mentioned in Scheme 80, anisole was brominated to **250a** in 82% yield

using [BMIM]NTf_2 as a solvent in 1.5 h (Table 9, entry 1). It was also found that bromination of anisole can be carried out using $FeCl_3$ (5 mol %) and a catalytic amount of [BMIM]NTf_2 (15 mol %) in *N*,*N*-dimethylformamide or toluene, giving **250a** in excellent yield with an increased reaction time of 2.5 h (entries 2 and 3). The reaction could be also performed with lower catalyst loading. For example, using $FeCl_3$ (2.5 mol %) and [BMIM]NTf_2 (7.5 mol %) in toluene gave 4-bromoanisole (**250a**) in 79% yield (entry 4).

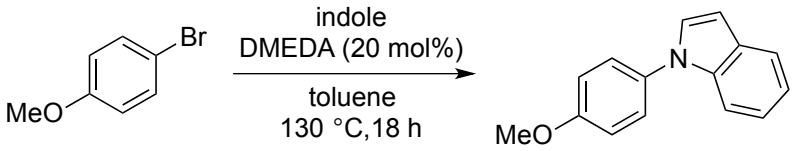


250a

Entry	$FeCl_3$ (mol %)	[BMIM]NTf_2 (mol %)	Solvent	Time (h)	Yield (%)
1	5	---	[BMIM]NTf_2	1.5	82
2	5	15	DMF	2.5	84
3	5	15	toluene	2.5	86
4	2.5	7.5	toluene	4	79

Table 9. Fe(III)-catalysed bromination of anisole in different solvents.

The *N*-arylation coupling step was then investigated. In toluene, a 30% conversion to **252a** was observed, when 4-bromoanisole (**250a**) was reacted with indole in the presence of $FeCl_3$ and Cu_2O (5 mol % each) at 110 °C (Table 10, entry 1). Increasing the catalyst loading to 10 mol % and the temperature to 130 °C, gave compound **252a** in 48% yield (entry 2). By changing the copper source to CuI and the base to cesium carbonate, a vastly improved yield of 95% for product **252a** was obtained (entry 3). The use of $Fe(NTf_2)_3$ is essential for effective bromination, especially with substrates containing strong deactivating groups. Therefore, the reaction was repeated using a catalytic amount of ionic liquid to examine its effect on the *N*-arylation reaction. In the presence of 30 mol % of [BMIM]NTf_2, compound **252a** was obtained in 78% yield (entry 4).

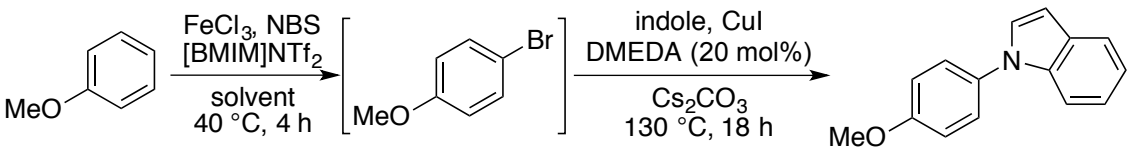


250a **252a**

Entry	$FeCl_3$ (mol %)	CuX (mol %)	[BMIM]NTf_2 (mol %)	Base (2 equiv.)	Conv. (%)[a]	Yield (%)
1[b]	5	Cu_2O (5)	---	K_3PO_4	30	---
2	10	Cu_2O (10)	---	K_3PO_4	63	48
3	10	CuI (10)	---	Cs_2CO_3	100	95
4	10	CuI (10)	30	Cs_2CO_3	100	78

Table 10. Optimisation of Cu(I)-catalysed *N*-arylation reaction. [a]Calculated from ^1H NMR spectrum of crude reaction mixture. [b]The reaction was performed at 110 °C.

Using these optimised conditions, the one-pot two-step process was attempted. Firstly, anisole was brominated in 2 h using $FeCl_3$ (10 mol %) and [BMIM]NTf_2 (30 mol %) in toluene. After completion, the Cu(I)-catalysed *N*-arylation reaction was performed. However, only 14% conversion was observed for the coupled product **252a** (Table 11, entry 1). Further reduction of the catalyst loading of $FeCl_3$ and [BMIM]NTf_2 in DMF or toluene led to improved conversions (entries 2 and 3). It was also noticed that the conversion remained the same when the reaction was left stirring for another 24 h. During the one-pot reaction, it was found that there was a solubility issue of the base in the reaction mixture. To solve this issue, water as a co-solvent was added to the reaction mixture. This allowed a better solubility of the base and all other reagents, giving the coupled product **252a** in nearly quantitative conversion (60% overall yield) (entry 4). Finally, by lowering the catalyst loading of $FeCl_3$ (2.5 mol %) and [BMIM]NTf_2 (7.5 mol %), a significant increase of yield (78%) to **252a** was obtained (entry 5).



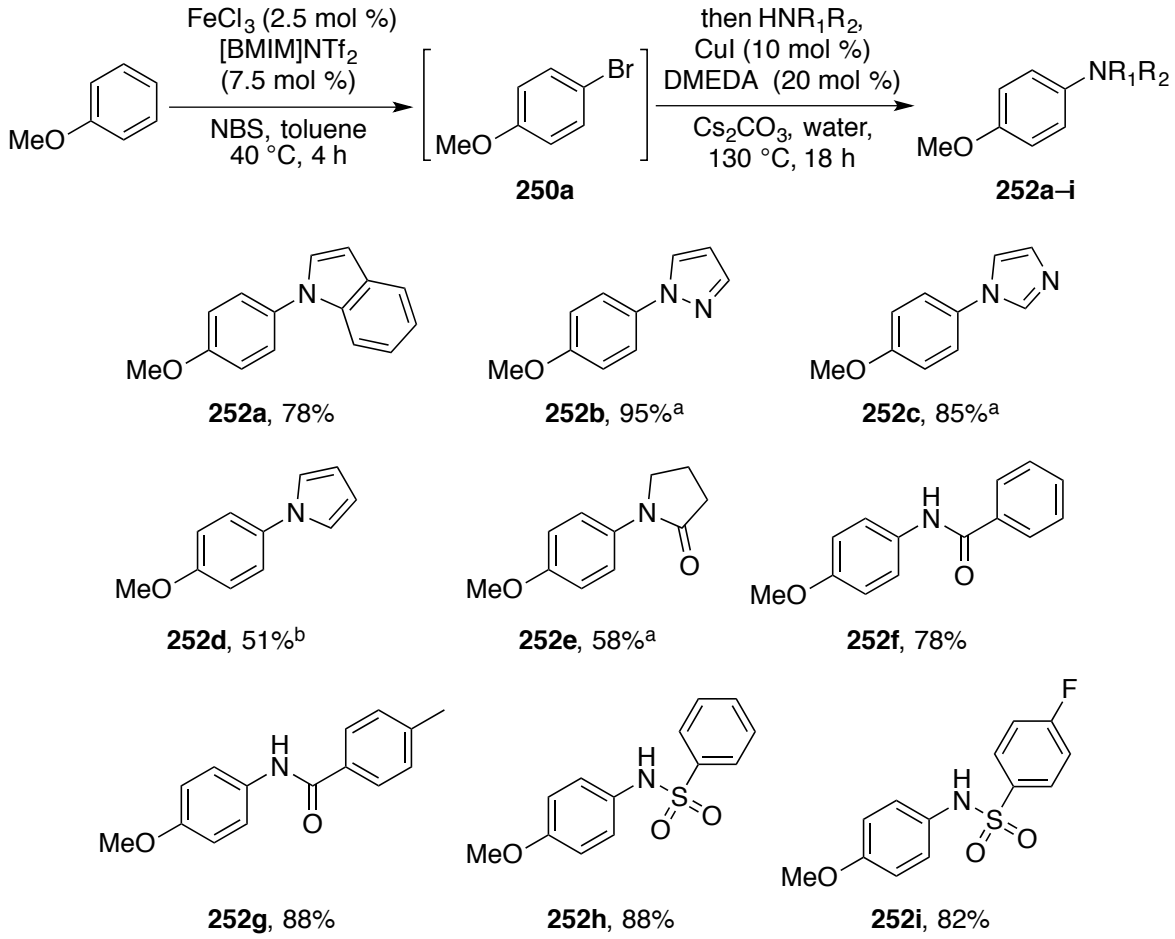
250a **252a**

Entry	$FeCl_3$ (mol %)	$[BMIM]NTf_2$ (mol %)	Solvent	Conv. (%)[a]	Yield (%)
1	10	30	toluene	14	---
2	5	15	DMF	39	---
3	5	15	toluene	45	---
4[b]	5	15	toluene	95	60
5[b]	2.5	7.5	toluene	95	78

Table 11. Optimisation of the one-pot *p*-amination process. [a]Calculated from ^1H NMR spectrum of crude reaction mixture. [b]Water (40% reaction volume) was added to the second step.

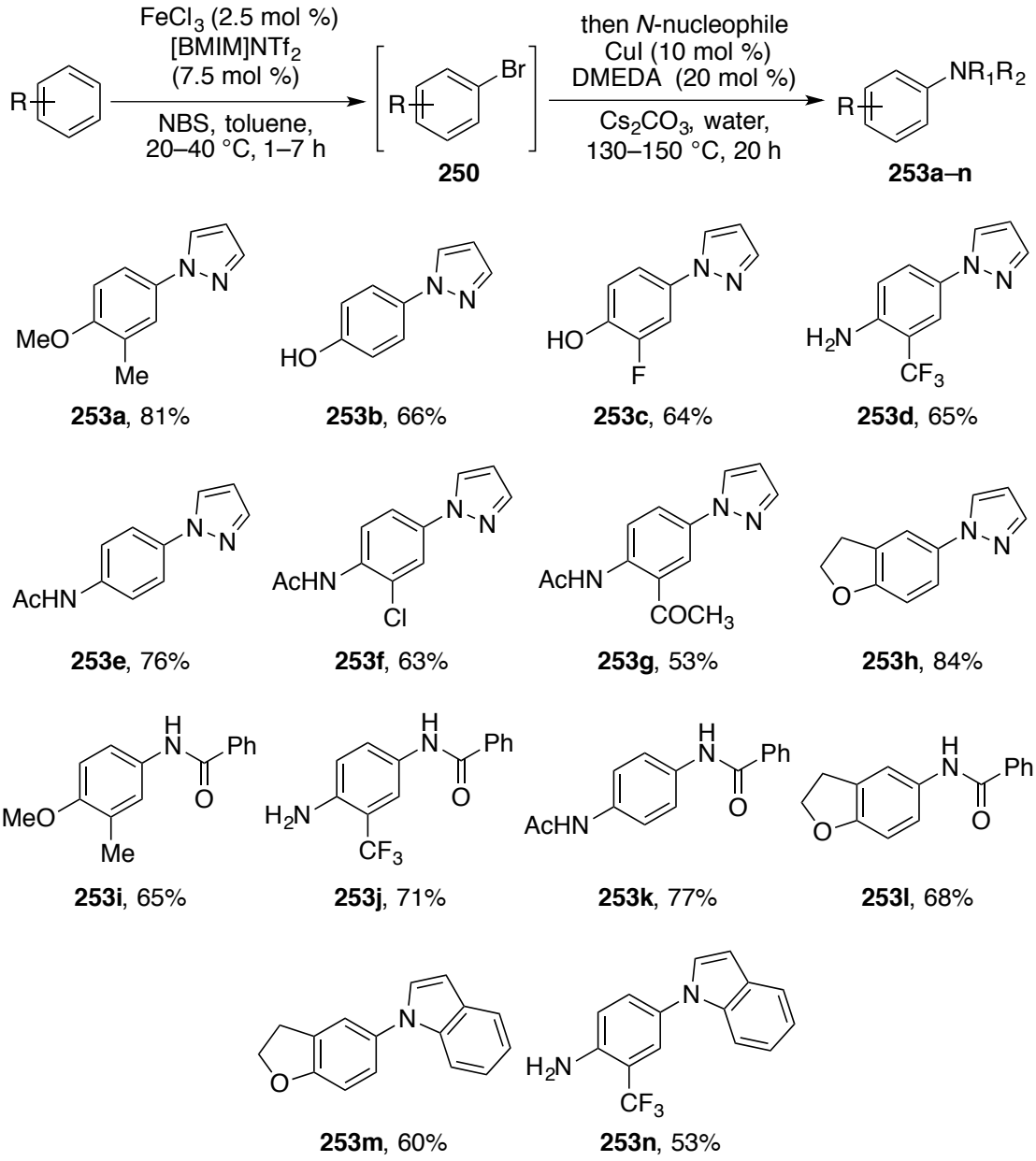
2.3.3.3 Substrate scope

Having identified the optimal conditions for the one-pot, two-step synthesis of product **252a**, the scope of the process was explored (Scheme 84). The bromination step was carried out using NBS in the presence of $FeCl_3$ (2.5 mol %) and $[BMIM]NTf_2$ (7.5 mol %). After completion, the nucleophilic partner, copper(I) iodide (10 mol %) as the catalyst, DMEDA (20 mol %) as the ligand and cesium carbonate were then added. Firstly, the scope of the one-pot process was explored using anisole with various *N*-heterocycles (e.g. indole, pyrazole, imidazole, pyrrole and pyrrolidin-2-one), amides and sulfonamides. This led to the formation of the corresponding *p*-aminated coupled products **252a–i** in excellent overall yields as single regioisomers. It was also found that pyrazole **252b** could be prepared in a multigram scale in almost quantitative yield.



Scheme 84: Scope of the one-pot *p*-amination process with anisole (250a). [a]*N*-Arylation reaction was performed at 150 °C for 24 h. [b]*N*-Arylation reaction was performed at 150 °C for 36 h.

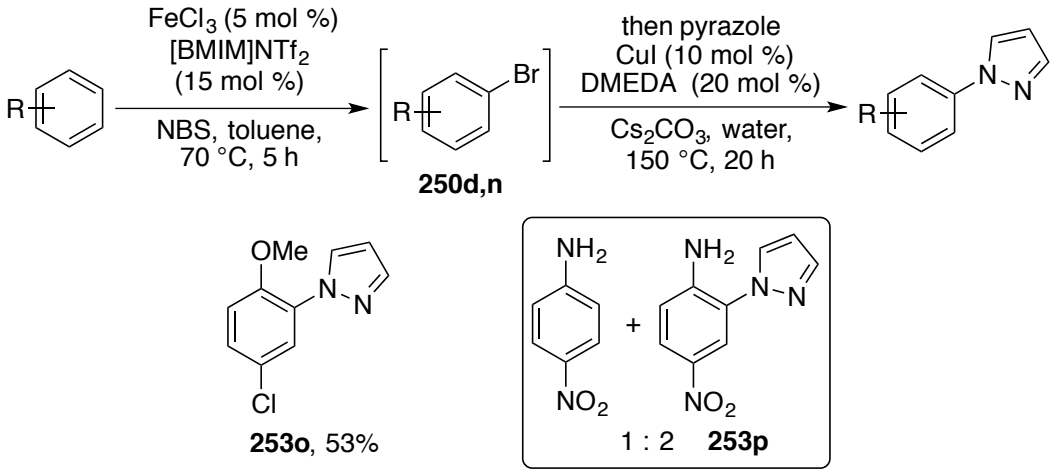
The scope of the one-pot process was further expanded to include different aryl substrates using pyrazole, benzamide and indole as nucleophilic partners (Scheme 85). High yields of the *para*-aminated products **253a–n** were afforded when the process was applied to aryl substrates such as anisole, phenol, aniline and acetanilide derivatives, in the presence of electron-donating or electron-withdrawing substituents. In addition, with substrates containing nucleophilic function groups (e.g., phenols and anilines), the process was found to be efficient and cleanly formed the *N*-coupled products in high yields as single regioisomers. For example, the one-pot synthesis of pyrazole **253d**, which contains a strong electron-deactivating group and also a nucleophilic function group, was achieved in 65% yield.



Scheme 85: Scope of the one-pot *p*-amination process with different aryl substrates.

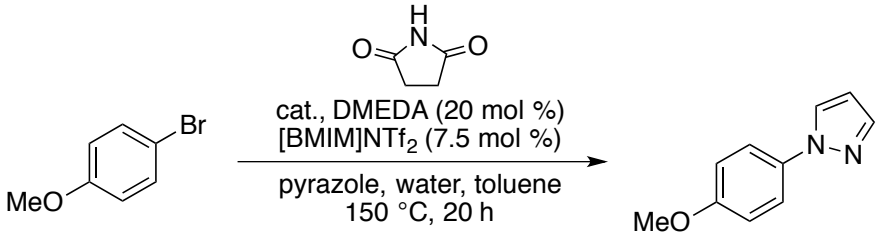
Another aim of this study was to investigate the one-pot *ortho*-bromination/*N*-arylation reaction (Scheme 86). More forcing conditions were required for both bromination and amination steps when the process was applied to 4-chloroanisole, giving the *ortho*-aminated coupled product **253o** in a 53% yield over the two-step process. In another attempt to include other substrates, a similar one-pot procedure was applied to 4-nitroaniline. However, this gave an inseparable mixture of both 4-nitroaniline starting material and the coupled product **253p** in a 1:2 ratio. Analysis of the ^{1}H NMR spectrum of the crude bromination reaction

showed complete conversion to the 2-bromo-4-nitroaniline (**250n**). However, the slower *N*-arylation reaction resulted in reduction of the organcopper intermediate of **250n** and led to regeneration of 4-nitroaniline. It was proposed that this could be assisted by the presence of the adjacent amine group.



Scheme 86: Preliminary study of a one-pot *ortho*-amination process.

Various methods have been reported for *N*-arylation reactions of aromatic halides with a wide range of *N*-nucleophiles using metal catalysts (most commonly copper).[150−153] Recently, Correa and Bolm have shown that iron(III) catalysts could influence the *N*-arylation reactions.[167,168] However, two years later Buchwald and Bolm reported that the reaction was essentially catalysed by copper contaminants.[169] Another study by Taillefer and co-workers has shown that both metals are essential for effective *N*-arylation reaction in an iron–copper co-catalysed process, in which neither of them could be used individually to effect the process.[170] To probe the role of each catalyst during the *N*-arylation reaction, 4-bromoanisole (**250a**) was subjected to series of reactions using pyrazole as a nucleophile (Table 12). It was found that less than 5% conversion was observed when iron(III) triflimide was employed individually as the catalyst (entry 1), while a 92% yield obtained for the coupled product **252b** with copper iodide (entry 2). By employing both catalysts, compound **252b** was afforded in 87% yield (entry 3). These results strongly confirmed the role of copper iodide to effect the *N*-arylation reaction.



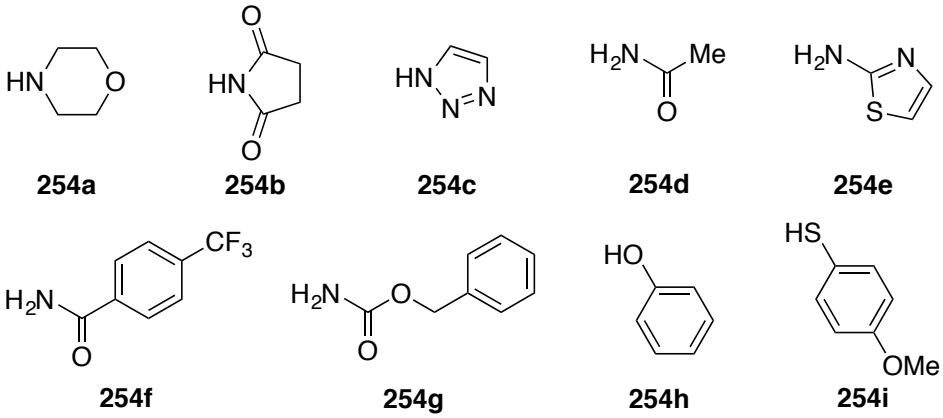
250a **252b**

Entry	Catalyst	Yield (%)
1	$FeCl_3$ (2.5 mol %)	<5
2	CuI (10 mol %)	92
3	$FeCl_3$ (2.5 mol %)/CuI (10 mol %)	87

Table 12: Investigation of the role of iron and copper catalysts during the *N*-arylation reaction.

2.3.3.4 Limitations

Limitations of this one-pot process were observed when using nitrogen nucleophiles such as morpholine (**254a**), succinimide (**254b**), 1*H*-1,2,3-triazole (**254c**), acetamide (**254d**), 2-aminothiazole (**254e**) and other nucleophiles with strong electron withdrawing group such as 4-(trifluoromethyl)benzamide (**254f**) (Figure 10). These attempts gave no products even when increasing temperature (150 °C), reaction time (up to 72 h), catalyst loading (up to 50 mol %) or using other ligands. Other nucleophiles such as benzyl carbamate (**254g**) gave traces of the coupled product (<10% conversion) with other unidentified by-products. Attempts were made to include oxygen (**254h**) or sulfur nucleophiles (**254i**). However, only de-bromination was observed.



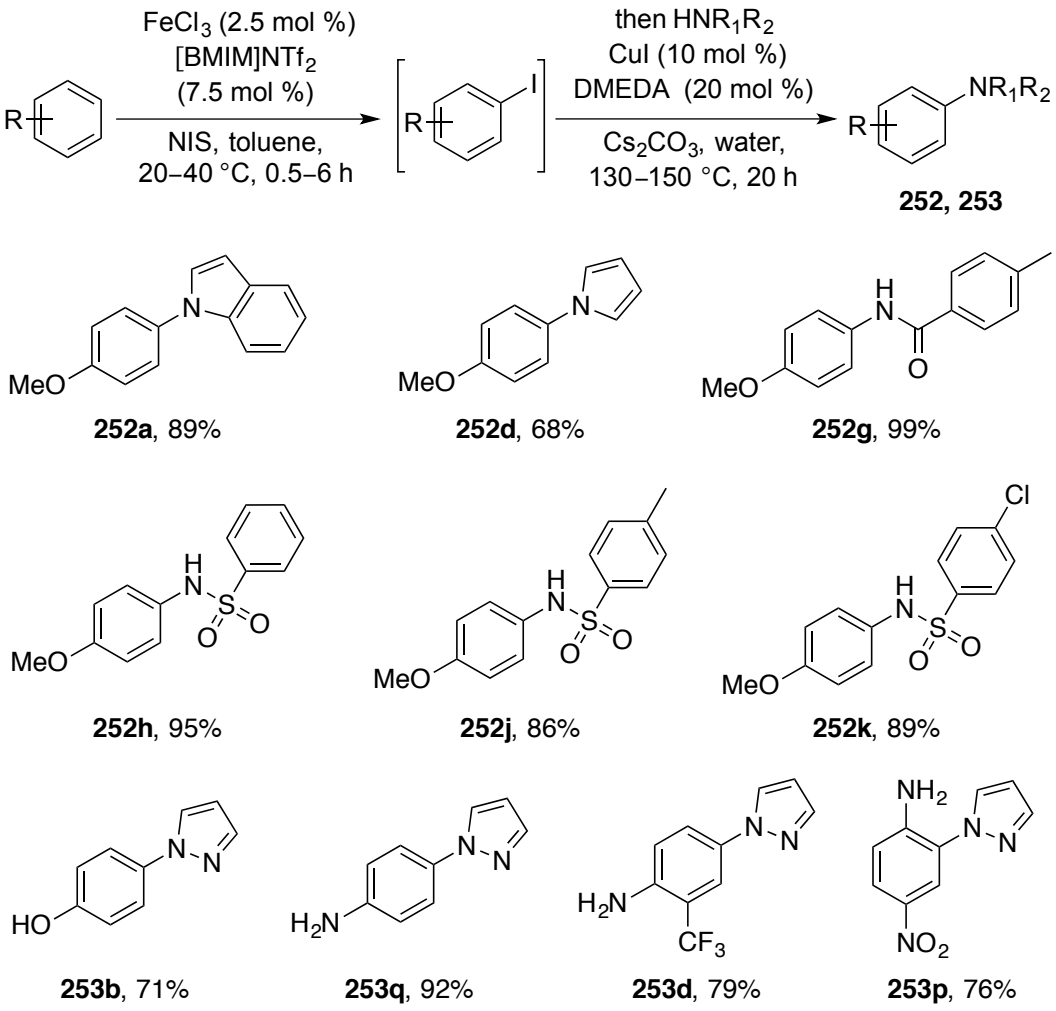
254a **254b** **254c** **254d** **254e**

254f **254g** **254h** **254i**

Figure 10: Unsuccessful nucleophiles.

2.3.4 One-pot iron(III)-catalysed iodination and copper(I)-catalysed *N*-arylation of aromatic compounds

Having had success with the one-pot *para*-amination process with a wide range of aromatic substrates and nucleophiles, another study was undertaken involving iodination of arenes with NIS followed by the C–N coupling reaction (Scheme 87). It was proposed that the weaker carbon-iodine bond could improve the efficiency of the one-pot process and further expand the scope. Using similar conditions to that described in Scheme 84, this modified one-pot process was initially applied to anisole and other aromatic substrates with different *N*-nucleophiles, giving the coupled products **252** and **253** in excellent yields. One of the advantages of using the iodination over the bromination was the formation of the *para*-aminated products in higher yields. For example, the one-pot iodination/*N*-arylation of anisole using indole or *p*-toluamide as nucleophiles gave **252a** and **252g** in 89% (previously, 78%) and 99% (previously, 88%) yields, respectively. Moreover, the one-pot iodination/*N*-arylation of aniline gave the coupled product **253q** in a 92% yield as a single regioisomer. It is worth mentioning that the bromination of aniline gave a mixture of mono-, di- and tri-brominated products (Scheme 81), while the iodination gave a single mono-iodinated regioisomer. During the one-pot *ortho*-bromination/*N*-arylation of 4-nitroaniline, an inseparable mixture of the coupled product **253p** and 4-nitroaniline starting material was formed (Scheme 86). However, by using the one-pot iodination/*N*-arylation process, compound **253p** was effectively and cleanly obtained in 76% yield. Work is underway by another PhD student (Martyn Henry) to further optimise the one-pot process to include other nucleophiles such as aliphatic amines, carbamates and intramolecular cyclisation for the *N*-arylation reaction.



Scheme 87: Scope of the one-pot iron-catalysed iodination and copper(I)-catalysed *N*-arylation process.

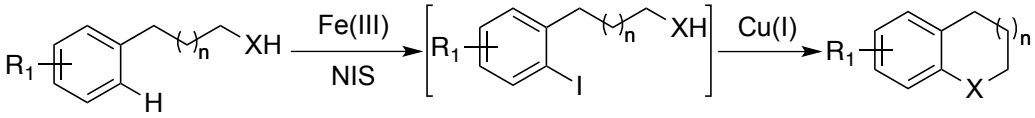
2.3.5 Conclusions and future work

In conclusion, an efficient and highly regioselective method for the bromination of arenes *via* iron(III) triflimide activation of NBS has been developed. This process was carried out using 5 mol % loading of inexpensive and environmentally friendly iron(III) chloride catalyst, as well as the use of a cheap and recyclable ionic liquid which acts as a solvent and as a source of triflimide to activate the iron catalyst. The use of this combination allowed the synthesis of a large library of brominated arenes **250** tolerating electron-rich and electron-deficient groups, in a short time under mild conditions.

Another aim of this study was to develop a one-pot two-step *p*-amination process involving the standard bromination method ($FeCl_3$ (5 mol %) in [BMIM]NTf_2 as a

solvent) in combination with a copper(I)-catalysed *N*-arylation reaction. However, no aminated products were detected. As the issue with the *N*-arylation reaction was associated with the use of ionic liquid as a solvent, a modified version of the bromination reaction using catalytic amounts of both $FeCl_3$ and [BMIM]NTf_2 in toluene was then developed. Combination of this modified transformation with the *N*-arylation reaction has allowed the synthesis of a large library of aminated aryl compounds (**252** and **253**) using different aryl substrates with a wide range of *N*-nucleophiles in high yields as single regioisomers.

Limitations of this one-pot process were observed when using other nitrogen nucleophiles such as aliphatic amines and carbamates. Therefore, another one-pot process was developed, which involved iodination of arenes with NIS followed by the C-N coupling reaction. Initially, this modified one-pot was applied to similar substrates and nucleophiles and allowed the synthesis of the coupled products in higher yields. Work is underway by another PhD student (Martyn Henry) to further optimise the one-pot process to include other nitrogen and oxygen nucleophiles and most importantly the development of a one-pot intramolecular amination and etherification process (Scheme 88).



X = NR or O
n = 0 or 1

Scheme 88: A one-pot iodination and amination or etherification process.

2.4 Iron(III)-catalysed chlorination of activated arenes

2.4.1 Introduction and aims

Aromatic chlorides are important synthetic blocks in organic synthesis, used as precursors for coupling and substitution reactions.[171–176] These compounds were found in a wide range of natural products,[177,178] e.g. nitrofungin (**255**),[179] 2,4-dichlorophenol (**256**)[180] and helitenuone (**257**),[181,182] and as a structural component in a number of medicinal compounds and agrochemicals, such as the antiseptic agent chloroxylenol (**258**),[183,184] the pesticide chloroxynil (**259**)[185,186] and the cholinesterase inhibitor **260** (Figure 11).[187]

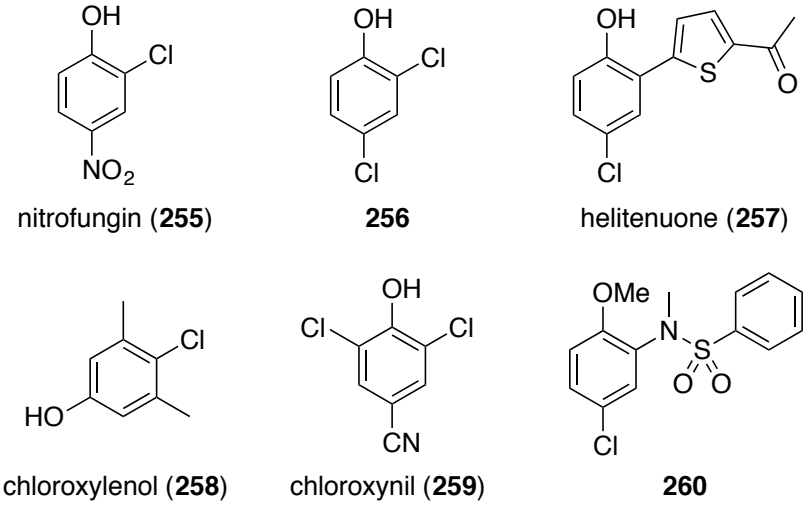
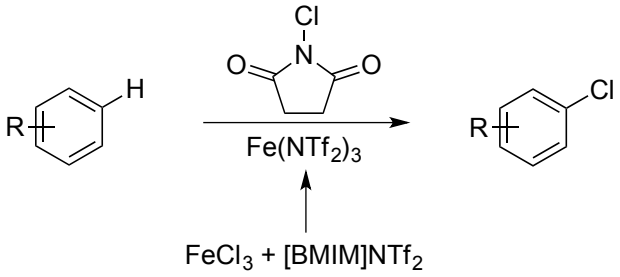


Figure 11: Biologically active chloroarenes.

It was previously shown (Section 2.3) the ability of iron triflimide, as a powerful Lewis acid, to activate NIS and NBS for a mild, efficient and highly regioselective halogenation of a wide range of aromatic compounds.[141a,145] It was proposed that this method could be further modified for chlorination of a variety of activated arenes. The first aim of this project was to develop an iron(III)-catalysed chlorination method using *N*-chlorosuccinimide (NCS) as the chlorinating reagent (Scheme 89). After exploring the scope of this transformation, the next aim of this study would be the development of a one-pot dihalogenation method of aromatic compounds. Based on the reactivity differences of carbon-halogen bonds, the synthetic utility of these dihalogenated products would then be examined in the synthesis of natural products and biologically important targets.

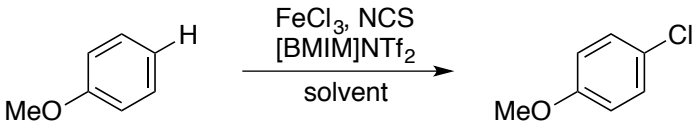


Scheme 89: Iron(III) triflimide catalysed chlorination.

2.4.2 Optimisation

The study started with screening the chlorination of anisole in different solvents (Table 13). It was previously shown the iron(III)-catalysed bromination of anisole using iron(III) chloride (5 mol %) in [BMIM]NTf_2 as a solvent (also as a source of triflimide to activate the iron(III) chloride catalyst). This transformation required a temperature of 40 °C and reaction time of 1.5 h. The same methodology was applied to the chlorination of anisole with NCS. It was found that a higher temperature of 50 °C and an increased reaction time of 5 h were required to give complete conversion to 4-chloroanisole (**261a**) (entry 1). This is due to the stronger nitrogen-chlorine bond of NCS. During previous investigation of the one-pot amination process (Section 2.3.3.2, Table 9), a modified procedure of the iron(III) triflimide bromination reaction using catalytic amounts of both $FeCl_3$ and [BMIM]NTf_2 in toluene or DMF was developed. Using a similar strategy, it was proposed that a catalytic version of the chlorination procedure could be achieved. Initially, anisole was subjected to chlorination reaction using iron(III) chloride (2.5 mol %) and [BMIM]NTf_2 (7.5 mol %) in *tert*-butyl methyl ether. However, this showed no conversion after stirring for 24 h at 50 °C (entry 2). Although the use of the ionic liquid as a solvent is essential for faster halogenation, the catalytic chlorination in toluene or THF gave **261a** in good conversion (60% and 75%, respectively) after 24 h (entry 3 and 4). It was noticed that there was a solubility issue of the NCS reagent in toluene, which resulted in low conversion to **261a** (compared to THF), even when increasing the temperature to 60 °C and reaction time to 48 h. On the other hand, with the use of THF as a solvent and a higher temperature of 60 °C, compound **261a** was formed in a 100% conversion after 18 h (entry 5). It was also found that the chlorination reaction could be completed in a

shorter reaction time (8 h) using higher catalyst loading of both $FeCl_3$ (5 mol %) and [BMIM]NTf_2 (15 mol %) (entry 6).



261a

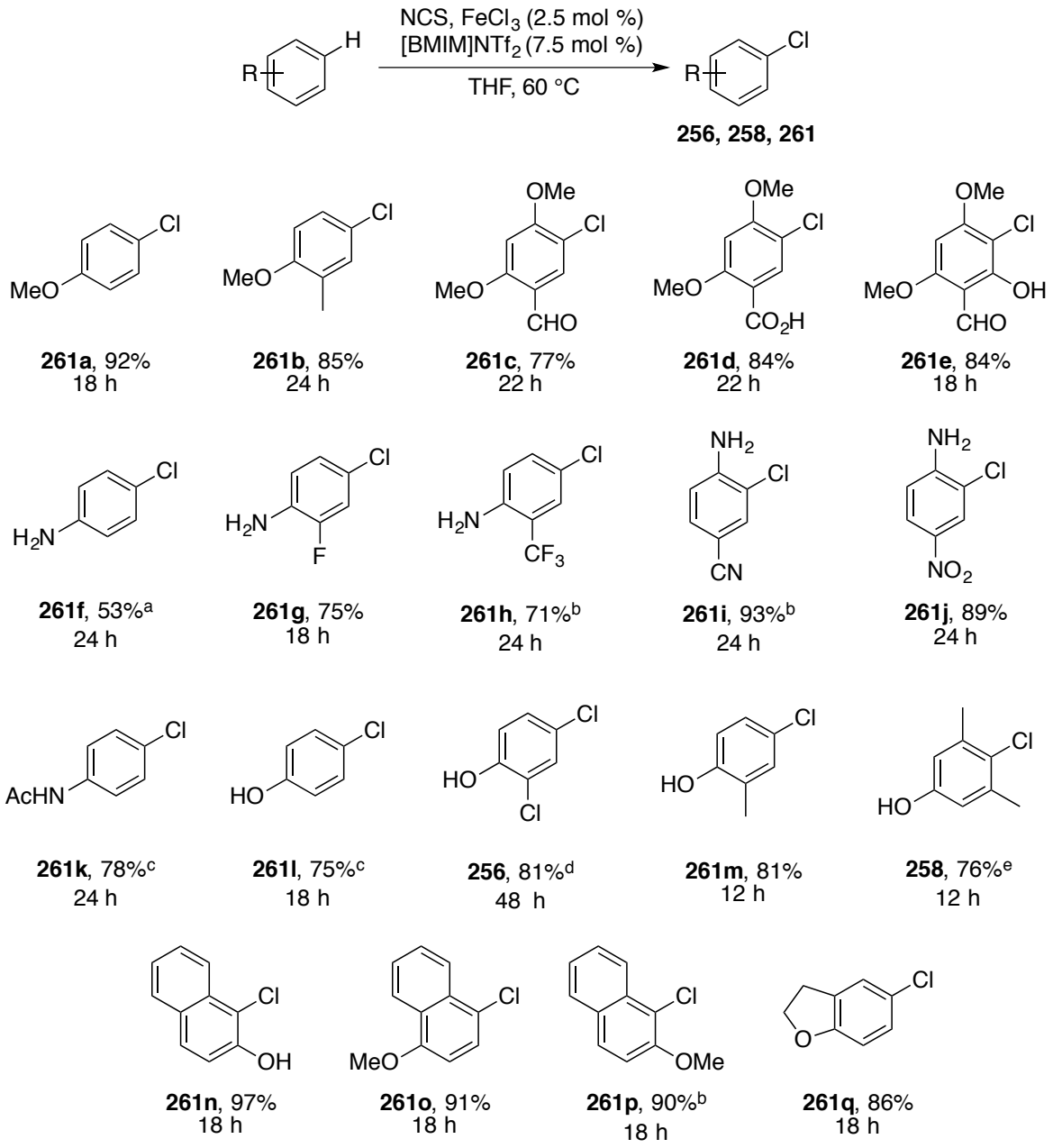
Entry	$FeCl_3$ (mol %)	[BMIM]NTf_2 (mol %)	Solvent	Temperature (°C)	Time (h)	Conversion (%)[a]
1	5	---	[BMIM]NTf_2	50	5	100
2	2.5	7.5	*t*-BuOMe	50	24	---
3	2.5	7.5	toluene	50	24	60
4	2.5	7.5	THF	50	24	75
5	2.5	7.5	THF	60	18	100
6	5	15	THF	60	8	100

Table 13. Optimisation of the iron(III) triflimide catalysed chlorination of anisole. [a]Calculated from ^{1}H NMR spectrum of crude reaction mixture.

2.4.3 Substrate scope

Having successfully optimised the conditions for the synthesis of 4-chloroanisole (**261a**), the scope of the process was then evaluated (Scheme 90). In general, the use of $FeCl_3$ (2.5 mol %) and [BMIM]NTf_2 (7.5 mol %) was found to be sufficient for effective chlorination of a wide range of compounds such as anisole, phenol and aniline derivatives, affording the corresponding chlorinated products in high yields. The only issue observed with this method was the chlorination of monosubstituted substrates such as aniline, acetanilide and phenol which gave the *ortho*-chlorinated regioisomer as a byproduct. In comparison to the iron(III)-catalysed bromination which only produced *para*-products. This is because of the smaller size of the chlorinating reagent compared to bromine, as well as the higher temperature used for this chlorination. However, the major *para*-products (**261f**, **261k** and **261l**) were easily separated from the side-products in good yields (53%, 78% and 75%, respectively), by column chromatography. Chlorination of multisubstituted substrates, naphthalenes and 2,3-dihydrobenzofuran produced the corresponding products (e.g. **261b–e, 261g**, **261n–p** and **261q**) in excellent

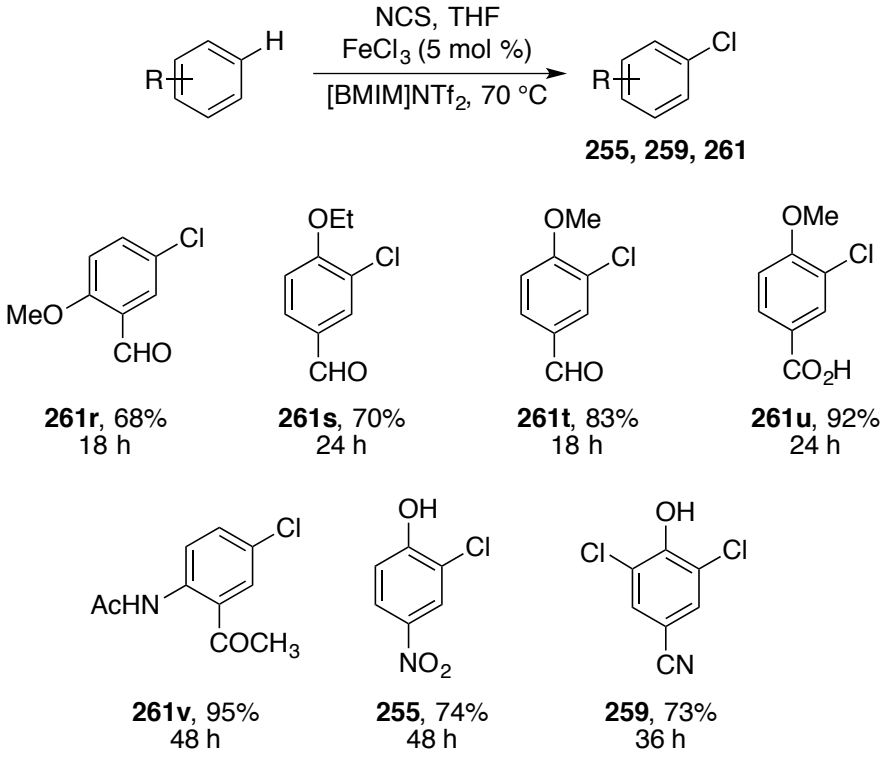
yields (77**–**97% yield) as single regioisomers. In addition, chlorination of substrates such as 4-nitroaniline gave the corresponding *ortho*-chlorinated product **261j** in high yield (89%). Other arenes with strong electron deactivating groups such as 2-(trifluoromethyl)aniline and 4-aminobenzonitrile required more forcing conditions {$FeCl_3$ (5 mol %) and [BMIM]NTf_2 (15 mol %), with a higher temperature of 70 °C} to give products **261h** and **261i** in full conversion. This method was then applied for the synthesis of important chlorine-containing compounds. For example, 4-chloro-2-methylphenol (**261m**),[188,189] a precursor used for the synthesis of 2-methyl-4-chlorophenoxyacetic acid (MCPA) and methyl chlorophenoxypropionic acid (MCPP) herbicides and the antiseptic agent, 4-chloro-3,5-dimethylphenol (chloroxylenol)[183,184] (**258**), were synthesised in 81% and 76% yields, respectively. Dichlorinated compounds could also be prepared using this method. For example, 2,4-dichlorophenol (**256**), a compound used as a growth hormone (isolated from soil *Penicillium*) and also a precursor of the herbicide, 2,4-dichlorophenoxy acetic acid (2,4-D), was synthesised in 81% yield from the reaction of phenol with two equivalents of NCS.[180]



Scheme 90: Scope of the iron(III)-catalysed chlorination process. [a]30% conversion to *ortho*-Cl isomer. [b]Reaction was performed at 70 °C using $FeCl_3$ (5 mol %) and [BMIM]NTf_2 (15 mol %). [c]20% conversion to *ortho*-Cl isomer. [d]Reaction was performed using 2 equivalent of NCS. [e]15% conversion to *ortho*-Cl isomer.

With substrates containing strong electron-withdrawing groups, low conversions were observed when using the previous procedure with a catalytic amount of [BMIM]NTf_2. As mentioned before, the electronic nature of the ionic liquid produces high cohesive pressure, which resulting in a faster reaction, in particular, with the chlorination of substrates containing deactivating groups. Therefore, an

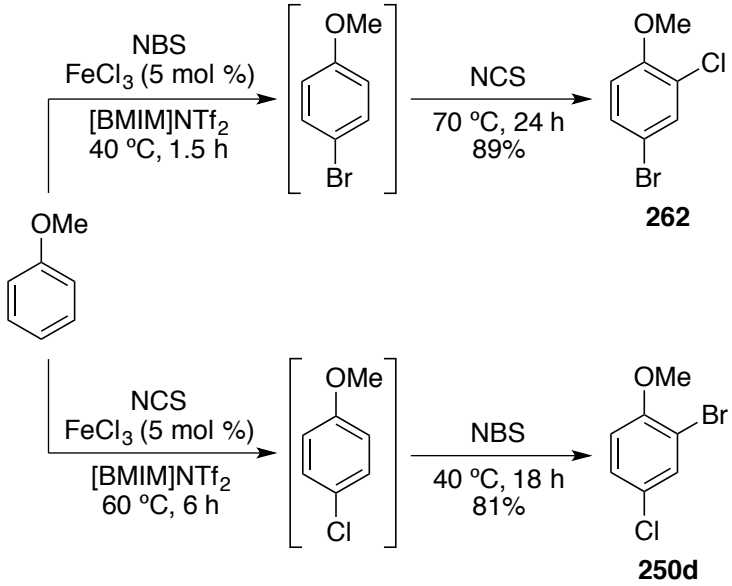
alternative procedure of using $FeCl_3$ (5 mol%) and [BMIM]NTf_2 as a solvent was utilised (Scheme 91). These conditions were found to fully chlorinate the deactivated substrates and gave the monochlorinated products **261r–v** in high yields at a higher temperature of 70 °C. Using this alternative method, the synthesis of 3-chloro-4-methoxybenzaldehyde (**261t**),[190] a metabolite isolated from soil *Lepista nuda*, and 2-chloro-4-nitrophenol (nitrofungin) (**255**),[179] an antimycotic drug was previously used in the treatment of fungal infections (isolated from *Stephanospora caroticolor*), were achieved in 83% and 74% yield, respectively. Under the same conditions, dichlorination of 4-hydroxybenzonitrile gave chloroxynil (**259**),[185,186] a commercially used nitrile herbicide in 73% yield after 36 h.



Scheme 91: Iron(III) triflimide catalysed chlorination of substrates containing deactivating groups in [BMIM]NTf_2 as a solvent.

2.4.4 The development of tandem dihalogenation processes

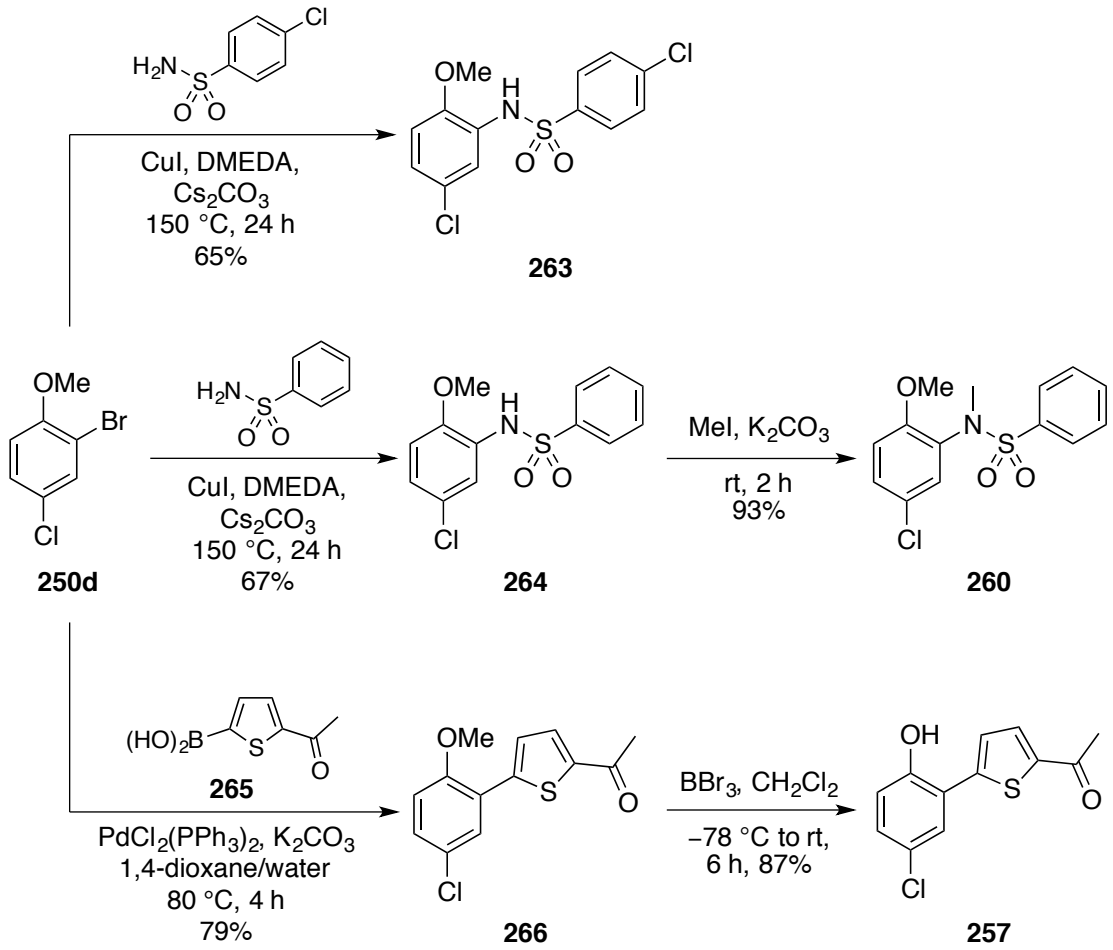
Another aim of this study was the development of a one-pot dihalogenation procedure for the synthesis of important intermediates for the preparation of biologically active compounds and natural products. As shown in Scheme 91, the iron(III) triflimide catalysed process was successfully used to prepare the dichlorinated product chloroxynil (**259**) cleanly in high yield. In a similar fashion, it was proposed that a single portion of iron(III) triflimide catalyst could be used to effect multiple halogenation reactions in a one-pot process. To investigate this procedure, anisole was initially subjected to a bromination reaction in the presence of $FeCl_3$ (5 mol %) and [BMIM]NTf_2 as the solvent (Scheme 92). This allowed the synthesis of 4-bromoanisole after 1.5 h. To the reaction mixture, NCS was then added and the reaction was left stirring at 70 °C for 24 h, giving the desired *ortho*-chlorinated product **262** in 89% overall yield. Another one-pot process initiated by a chlorination reaction and followed by bromination was also developed. The chlorination of anisole was performed at a 60 °C to cleanly form 4-chloroanisole. This was followed by the addition of NBS to give 2-bromo-4-chloroanisole (**250d**) in 81% yield as a single regioisomer. The synthesis of **250d** was also performed on a multigram scale using the one-pot two-step approach.



Scheme 92: One-pot iron(III)-catalysed dihalogenation processes.

2.4.4.1 Application of 2-bromo-4-chloroanisole (250d) in the synthesis of biologically important targets

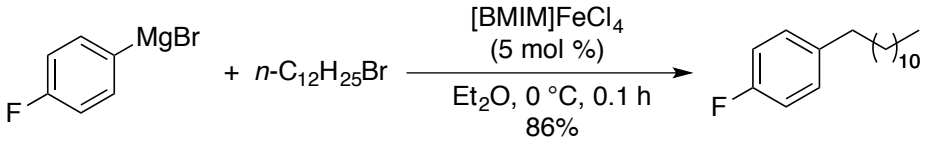
After the successful preparation of **250d** through the one-pot tandem process, the next stage of this study was to use this compound as a key building block in the synthesis of biologically important targets (Scheme 93). This could be achieved through selective functionalisation of the C–Br bond, relying on the difference in reactivity with the C–Cl bond. During previous investigation of the *ortho*-amination process (Section 2.3.3.3, Scheme 86), it was shown the ability of *ortho*-brominated products to effectively undergo a copper(I)-catalysed *N*-arylation reaction. Under similar conditions and by using 4-chlorobenzenesulfonamide as a nucleophile, 4-bromo-2-chloroanisole (**250d**) was successfully aminated to give the antibacterial compound **263**,[191] in 65% yield. A similar reaction of **250d** with benzenesulfonamide gave **264** in 67% yield. Compound **264** then underwent a *N*-methylation reaction to produce cholinesterase inhibitor **260** in 93% yield.[187] The synthetic utility of 4-bromo-2-chloroanisole (**250d**) was further explored for the synthesis of helitenuone (**257**),[181] a compound isolated from *Helichrysum* species. The synthesis of **257** began with a Suzuki-Miyaura reaction of 4-bromo-2-chloroanisole (**250d**) with commercially available 5-acetylthiophene-2-boronic acid (**265**), giving **266** in 79% yield. The hydroxyl group of **266** was then deprotected using boron tribromide to complete the synthesis of helitenuone (**257**) in 87% yield. The total synthesis of the natural product **257** was achieved in 56% overall yield from anisole, compared to the only reported method by Bohlmann and co-workers, which involved a six-step route and 7% overall yield.[182]



Scheme 93: Exploring the synthetic utility of 2-bromo-4-chloroanisole (250d) in the synthesis of natural products and biologically active targets.

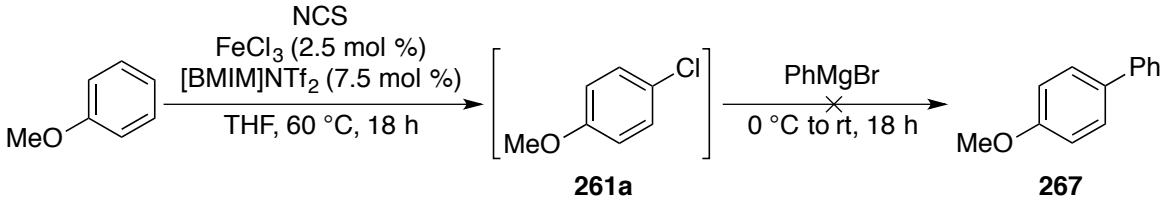
2.4.5 Attempted one-pot iron(III)-catalysed chlorination and Grignard cross-coupling reaction

Iron as an environmentally friendly catalyst has drawn attention of chemists, as a good alternative to other toxic and expensive late-transition metals, in cross-coupling reactions.[192–194] The next aim of this study was to develop a one-pot process, involving iron(III) triflimide catalysed chlorination and Grignard cross-coupling of arenes. In 2006, Bica and Gaertner showed that an iron-containing ionic liquid, [BMIM]$FeCl_4$, could be used to catalyse aryl Grignard cross-coupling with various alkyl halides (Scheme 94).[195]



Scheme 94: Grignard cross-coupling reaction using iron-containing ionic liquid.

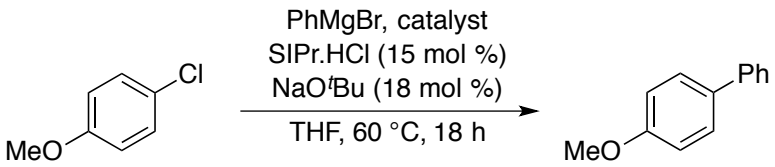
In a similar way, it was proposed that $Fe(NTf_2)_3$ (generated *in situ* from the reaction of $FeCl_3$ and $[BMIM]NTf_2$) could be used to effect both chlorination and Grignard cross-coupling reactions in a one-pot process. In an attempt to use similar conditions, anisole was first subjected to a chlorination reaction using $FeCl_3$ (2.5 mol %) and $[BMIM]NTf_2$ (7.5 mol %) in THF. After completion, phenylmagnesium bromide was added at 0 °C. However, this showed no reaction (Scheme 95).



Scheme 95: First attempted one-pot process involving chlorination and Grignard cross-coupling reaction.

An optimisation of the Grignard cross-coupling reaction using 4-chloroanisole (**261a**) was then carried out (Table 14). In 2014, Chua and Duong reported a successful Grignard cross-coupling reaction using various iron catalysts in the presence of 1,3-bis-(2,6-diisopropylphenyl)imidazolinium chloride (SIPr.HCl) as a ligand and sodium *tert*-butoxide as a base.[196] During the optimisation of the Grignard reaction, the effect of the ionic liquid and *N*-succinimide (generated from the chlorination reaction) was investigated. Under similar conditions,[196] it was found that there were no conversion observed to **267** when both the ionic liquid and *N*-succinimide (one equivalent) existed in the reaction mixture (entries 1, 2 and 3). The use of only $FeCl_3$ (2.5 mol %) gave biaryl **267** in 62% conversion (entry 4). The reaction was further improved when doubling the catalyst loading to 5 mol %, giving **267** in 80% yield (entry 5). As a result, it was found that there was no way to perform the one-pot process, as the $[BMIM]NTF_2$ is essential for the chlorination reaction, as well as the issue with *N*-succinimide that is generated

from the chlorination reaction.



261a **267**

Entry	$FeCl_3$ (mol %)	[BMIM]NTF_2 (mol %)	Additives	Conversion (%)	Yield (%)
1	2.5	7.5	*N*-succinimide	No reaction	---
2	2.5	7.5	---	No reaction	---
3	2.5	---	*N*-succinimide	No reaction	---
4	2.5	---	---	62	---
5	5	---	---	89	80

Table 14: Attempted Grignard cross-coupling reaction of 4-chloroanisole (261a).

2.4.6 Conclusions

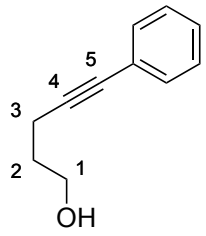
In conclusion, a highly regioselective chlorination method of aromatic compounds *via* iron(III) triflimide activation of NCS have been developed. In general, the use of catalytic amounts of both $FeCl_3$ (2.5 mol %) and [BMIM]NTf_2 (7.5 mol %) was found to be sufficient for effective chlorination of most substrates with a wide range of functional groups, giving the chlorinated products in high yields. Chlorination of deactivated substrates required more forcing conditions (higher catalyst loading, 5 mol %, and the use of the ionic liquid as a solvent), with a higher temperature of 70 °C. In addition, one-pot iron(III)-catalysed dihalogenation procedures for efficient preparation of dihalogenated products **250d** and **262** were developed. The synthetic utility of compound **250d** was demonstrated with the synthesis of chlorine-containing natural products, **257**, **260** and **263**. Finally, a one-pot iron(III)-catalysed chlorination and Grignard cross-coupling reaction was attempted. However, this failed to give any coupled products. The issue with this process was associated with the use of the ionic liquid, as well as the *N*-succinimide that was generated from the chlorination reaction.

3.0 Experimental

General Experimental

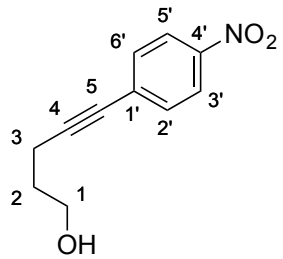
All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 or 500 spectrometer with chemical shift values in ppm relative to tetramethylsilane (δ_H 0.00 and δ_C 0.0) or residual chloroform (δ_H 7.26) and $CDCl_3$ (δ_C 77.2) as standard. Proton and carbon assignments are based on two-dimensional COSY and DEPT experiments, respectively. Mass spectra were obtained using a JEOL JMS-700 spectrometer for EI and CI or a Bruker Microtof-q for ESI. Infrared spectra were obtained neat using a Shimadzu IRPrestige-21 spectrometer. Melting points were determined on a Reichert platform melting point apparatus.

5-Phenylpent-4-yn-1-ol (169)[197]



Bis(triphenylphosphine)palladium(II) dichloride (0.022 g, 0.031 mmol) and copper iodide (0.012 g, 0.062 mmol) were dissolved in triethylamine (43 mL) and iodobenzene (0.42 mL, 3.7 mmol) was added and stirred at room temperature for 0.1 h. 4-Pentyn-1-ol (**168**) (0.26 g, 3.1 mmol) was added and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated *in vacuo*. Purification of the resulting residue by flash column chromatography (petroleum ether/ethyl acetate, 3:1) gave 5-phenylpent-4-yn-1-ol (**169**) (0.48 g, 95%) as a colourless oil. Spectroscopic data was consistent with the literature.[197] δ_H (400 MHz, $CDCl_3$) 1.59 (1H, br s, OH), 1.86 (2H, quin, *J* 6.5 Hz, 2-H_2), 2.54 (2H, t, *J* 6.5 Hz, 3-H_2), 3.82 (2H, t, *J* 6.5 Hz, 1-H_2), 7.24–7.30 (3H, m, 3 × ArH), 7.36–7.42 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 16.0 (CH_2), 31.4 (CH_2), 61.7 (CH_2), 81.1 (C), 89.4 (C), 123.8 (C), 127.7 (CH), 128.2 (2 × CH), 131.6 (2 × CH); *m/z* (CI) 161 (MH^+. 100%), 133 (20), 117 (28), 113 (13), 85 (28), 69 (39).

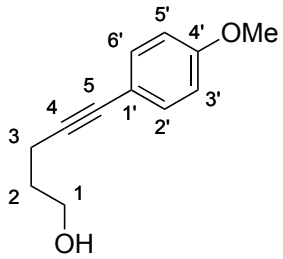
5-(4'-Nitrophenyl)pent-4-yn-1-ol (170)[198]



5-(4'-Nitrophenyl)pent-4-yn-1-ol (**170**) was synthesised as described for 5-phenylpent-4-yn-1-ol (**169**) using 4-pentyn-1-ol (**168**) (0.260 g, 3.09 mmol) and 4-iodo-1-nitrobenzene (0.920 g, 3.71 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 3:1) gave 5-(4'-nitrophenyl)pent-4-yn-1-ol (**170**) (0.627 g, 99%) as an orange solid. Mp 30–32 °C; Spectroscopic data was consistent with the literature.[198] δ_H (500 MHz, $CDCl_3$) 1.44 (1H, br t, *J* 6.8 Hz,

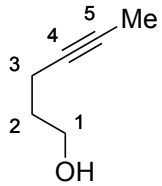
OH), 1.89 (2H, quin, *J* 6.8 Hz, 2-H_2), 2.59 (2H, t, *J* 6.8 Hz, 3-H_2), 3.82 (2H, q, *J* 6.8 Hz, 1-H_2), 7.49–7.54 (2H, m, 2'-H and 6'-H), 8.13–8.18 (2H, m, 3'-H and 5'-H); δ_C (126 MHz, $CDCl_3$) 16.1 (CH_2), 31.1 (CH_2), 61.3 (CH_2), 79.5 (C), 95.9 (C), 123.4 (2 × CH), 130.9 (C), 132.2 (2 × CH), 146.5 (C); *m/z* (ESI) 228 (MNa^+. 100%), 199 (11), 176 (14), 166 (15), 152 (37), 144 (22), 138 (16), 102 (15).

5-(4'-Methoxyphenyl)pent-4-yn-1-ol (171)[199]



5-(4'-Methoxyphenyl)pent-4-yn-1-ol (**171**) was synthesised as described for 5-phenylpent-4-yn-1-ol (**169**) using 4-pentyn-1-ol (**168**) (0.260 g, 3.09 mmol) and 4-iodoanisole (0.870 g, 3.71 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave 5-(4'-methoxyphenyl)pent-4-yn-1-ol (**171**) (0.576 g, 95%) as a colourless oil. Spectroscopic data was consistent with the literature.[199] δ_H (400 MHz, $CDCl_3$) 1.54 (1H, br t, *J* 6.8 Hz, OH), 1.85 (2H, quin, *J* 6.8 Hz, 2-H_2), 2.52 (2H, t, *J* 6.8 Hz, 3-H_2), 3.80 (3H, s, OCH_3), 3.82 (2H, q, *J* 6.8 Hz, 1-H_2), 6.78–6.84 (2H, m, 3'-H and 5'-H), 7.30–7.35 (2H, m, 2'-H and 6'-H); δ_C (126 MHz, $CDCl_3$) 15.9 (CH_2), 31.5 (CH_2), 55.2 (CH_3), 61.4 (CH_2), 80.8 (C), 87.9 (C), 113.9 (2 × CH), 116.0 (C), 132.9 (2 × CH), 159.1 (C); *m/z* (EI) 190 (M^+. 100%), 159 (24), 145 (75), 134 (55), 115 (38), 83 (59), 75 (23), 47 (16).

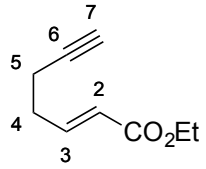
Hex-4-yne-1-ol (173)[107]



To a solution of 5-hexyn-1-ol (**172**) (0.200 g, 2.04 mmol) in dimethyl sulfoxide (7 mL) was added potassium *tert*-butoxide (0.460 g, 4.08 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by

the addition of 2 M hydrochloric acid and then extracted with diethyl ether (4 × 25 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave hex-4-yne-1-ol (**173**) (0.185 g, 92%) as a yellow oil. Spectroscopic data was consistent with the literature.[107] δ_H (400 MHz, $CDCl_3$) 1.56 (1H, br s, OH), 1.73 (2H, quin, *J* 6.2 Hz, 2-H_2), 1.78 (3H, t, *J* 2.6 Hz, 6-H_3), 2.22–2.29 (2H, m, 3-H_2), 3.75 (2H, t, *J* 6.2 Hz, 1-H_2); δ_C (126 MHz, $CDCl_3$) 3.4 (CH_3), 15.3 (CH_2), 31.5 (CH_2), 61.7 (CH_2), 76.1 (C), 78.5 (C); *m/z* (CI) 99 (MH^+. 100%), 81 (10), 73 (15), 71 (8), 69 (7).

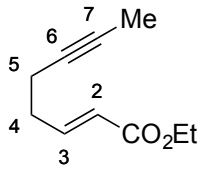
Ethyl (2*E*)-hept-2-en-6-ynoate (174)[200]



Dimethyl sulfoxide (3.16 mL, 44.5 mmol) was added to a stirred solution of oxalyl chloride (2.11 mL, 25.0 mmol) in dichloromethane (90 mL) at −78 °C. The mixture was stirred for 0.3 h before 4-pentyn-1-ol (**168**) (1.50 g, 17.8 mmol) in dichloromethane (20 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (12.5 mL, 89.0 mmol) was added. This reaction mixture was stirred for 0.5 h at −78 °C and then allowed to warm to room temperature and stirred for a further 3 h. A solution of lithium chloride (1.36 g, 32.0 mmol), triethyl phosphonoacetate (6.35 mL, 32.0 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (4.79 mL, 32.0 mmol) in acetonitrile (60 mL) was then prepared and stirred for 1 h. The Swern solution was concentrated *in vacuo*, then the Horner Wadsworth Emmons solution was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with a saturated solution of ammonium chloride (45 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (4 × 60 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated to give an orange oil. Purification by flash column chromatography (petroleum ether/diethyl ether, 7:3) gave ethyl (2*E*)-hept-2-en-6-ynoate (**174**) (2.45 g, 91%) as a yellow oil. Spectroscopic data was consistent with the literature.[200] δ_H (400 MHz, $CDCl_3$) 1.30

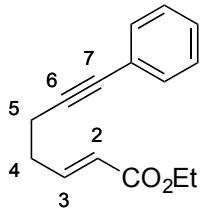
(3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.01 (1H, t, *J* 2.5 Hz, 7-H), 2.34–2.39 (2H, m, 5-H_2), 2.41–2.48 (2H, m, 4-H_2), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.90 (1H, dt, *J* 15.7, 1.5 Hz, 2-H), 6.97 (1H, dt, *J* 15.7, 6.7 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.3 (CH_3), 17.4 (CH_2), 31.0 (CH_2), 60.3 (CH_2), 69.4 (CH), 82.7 (C), 122.6 (CH), 146.3 (CH), 166.4 (C); *m/z* (CI) 153 (MH^+. 100%), 139 (5), 113 (10), 97 (5), 81 (15), 69 (15).

Ethyl (2*E*)-oct-2-en-6-ynoate (175)



Ethyl (2*E*)-oct-2-en-6-ynoate (**175**) was synthesised as described for ethyl (2*E*)-hept-2-en-6-ynoate (**174**) using hex-4-yne-1-ol (**173**) (0.170 g, 1.68 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 8:2) gave ethyl (2*E*)-oct-2-en-6-ynoate (**175**) (0.266 g, 95%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2921 (CH), 1721 (C=O), 1657, 1368, 1265, 1157, 1039, 975; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.77 (3H, t, *J* 2.3, 8-H_3), 2.25–2.32 (2H, m, 5-H_2), 2.34–2.41 (2H, m, 4-H_2), 4.19 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.87 (1H, dt, *J* 15.7, 1.5 Hz, 2-H), 6.98 (1H, dt, *J* 15.7, 6.6 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 3.4 (CH_3), 14.2 (CH_3), 17.7 (CH_2), 31.6 (CH_2), 60.2 (CH_2), 76.6 (C), 77.5 (C), 122.1 (CH), 147.1 (CH), 166.5 (C); *m/z* (ESI) 189.0883 (MNa^+. $C_{10}H_{14}NaO_2$ requires 189.0886).

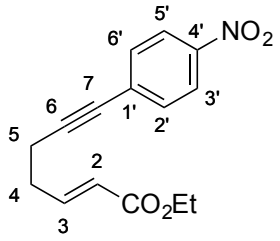
Ethyl (2*E*)-7-phenylhept-2-en-6-ynoate (176)[201]



Ethyl (2*E*)-7-phenylhept-2-en-6-ynoate (**176**) was synthesised as described for ethyl (2*E*)-hept-2-en-6-ynoate (**174**) using 5-phenylpent-4-yn-1-ol (**169**) (0.640 g, 3.96 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 17:3) gave ethyl (2*E*)-7-phenylhept-2-en-6-ynoate (**176**) (0.858 g, 95%) as a

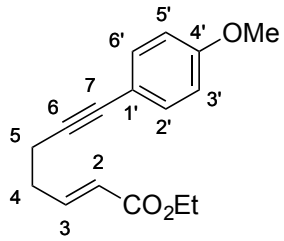
yellow oil. Spectroscopic data was consistent with the literature.[201] δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.47–2.61 (4H, m, 4-H_2 and 5-H_2), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.93 (1H, dt, *J* 15.7, 1.5 Hz, 2-H), 7.04 (1H, dt, *J* 15.7, 6.6 Hz, 3-H), 7.26–7.31 (3H, m, 3 × ArH), 7.36–7.41 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 18.4 (CH_2), 31.4 (CH_2), 60.2 (CH_2), 81.7 (C), 88.3 (C), 122.5 (CH), 123.6 (C), 127.8 (CH), 128.2 (2 × CH), 131.6 (2 × CH), 146.6 (CH), 166.3 (C); *m/z* (CI) 229 (MH^+. 100%), 155 (7), 113 (13), 81 (25), 69 (34).

Ethyl (2*E*)-7-(4'-nitrophenyl)hept-2-en-6-ynoate (177)



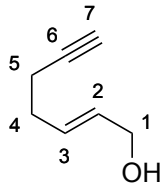
Ethyl (2*E*)-7-(4'-nitrophenyl)hept-2-en-6-ynoate (**177**) was synthesised as described for ethyl (2*E*)-hept-2-en-6-ynoate (**174**) using 5-(4'-nitrophenyl)pent-4-yn-1-ol (**170**) (0.460 g, 2.24 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 8:2) gave ethyl (2*E*)-7-(4'-nitrophenyl)hept-2-en-6-ynoate (**177**) (0.582 g, 95%) as a yellow solid. Mp 56–58 ºC; ν_{max}/cm^{-1} (neat) 2960 (CH), 1714 (C=O), 1591 (C=C), 1509, 1340, 1154, 854, 750; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.50–2.57 (2H, m, 4-H_2), 2.60–2.66 (2H, m, 5-H_2), 4.21 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.94 (1H, dt, *J* 15.7, 1.5 Hz, 2-H), 7.02 (1H, dt, *J* 15.7, 6.7 Hz, 3-H), 7.49–7.54 (2H, m, 2'-H and 6'-H), 8.14–8.18 (2H, m, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 18.6 (CH_2), 30.9 (CH_2), 60.4 (CH_2), 80.3 (C), 94.3 (C), 122.8 (CH), 123.5 (2 × CH), 130.6 (C), 132.3 (2 × CH), 146.0 (CH), 146.8 (C), 166.3 (C); *m/z* (ESI) 296.0881 (MNa^+. $C_{15}H_{15}NNaO_4$ requires 296.0893).

Ethyl (2*E*)-7-(4'-methoxyphenyl)hept-2-en-6-ynoate (178)[201]



Ethyl (2*E*)-7-(4'-methoxyphenyl)hept-2-en-6-ynoate (**178**) was synthesised as described for ethyl (2*E*)-hept-2-en-6-ynoate (**174**) using 5-(4'-methoxyphenyl)pent-4-yn-1-ol (**171**) (0.550 g, 2.89 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 8:2) gave ethyl (2*E*)-7-(4'-methoxyphenyl)hept-2-en-6-ynoate (**178**) (0.702 g, 94%) as a yellow oil. Spectroscopic data was consistent with the literature.[201] δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.46–2.59 (4H, m, 4-H_2 and 5-H_2), 3.80 (3H, s, OCH_3), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.92 (1H, dt, *J* 15.7, 1.5 Hz, 2-H), 6.79–6.84 (2H, m, 3'-H and 5'-H), 7.03 (1H, dt, *J* 15.7, 6.5 Hz, 3-H), 7.30–7.35 (2H, m, 2'-H and 6'-H); δ_C (126 MHz, $CDCl_3$) 14.3 (CH_3), 18.4 (CH_2), 31.5 (CH_2), 55.2 (CH_3), 60.3 (CH_2), 81.4 (C), 86.7 (C), 113.8 (2 × CH), 115.7 (C), 122.4 (CH), 132.9 (2 × CH), 146.8 (CH), 159.2 (C), 166.4 (C); *m/z* (EI) 258 (M^+. 22%), 230 (20), 185 (27), 145 (100), 130 (6), 102 (13), 83 (11).

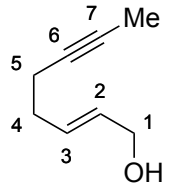
(2*E*)-Hept-2-en-6-yn-1-ol (179)[202a]



Ethyl (2*E*)-hept-2-en-6-ynoate (**174**) (2.28 g, 15.0 mmol) was dissolved in diethyl ether (80 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (33.0 mL, 33.0 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 3 h, before warming to room temperature overnight. The solution was cooled to 0 °C and quenched by the addition of a saturated solution of Rochelle salt (50 mL) and warmed to room temperature with vigorous stirring for 1 h, producing a white precipitate that was filtered through a pad of Celite® and washed with diethyl ether

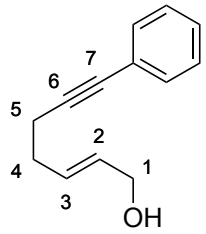
(3 × 75 mL). The filtrate was then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 1:1) gave (2*E*)-hept-2-en-6-yn-1-ol (**179**) (1.44 g, 87%) as a pale yellow oil. Spectroscopic data was consistent with the literature.[202a] δ_H (500 MHz, $CDCl_3$) 1.42 (1H, br s, OH), 1.99 (1H, t, *J* 2.5 Hz, 7-H), 2.28–2.33 (4H, m, 4-H_2 and 5-H_2), 4.14 (2H, d, *J* 4.0 Hz, 1-H_2), 5.70–5.81 (2H, m, 2-H and 3-H); δ_C (126 MHz, $CDCl_3$) 18.5 (CH_2), 31.1 (CH_2), 63.5 (CH_2), 68.8 (CH), 83.7 (C), 130.5 (CH), 130.6 (CH); *m/z* (CI) 111 (MH^+. 3%), 107 (15), 93 (100), 81 (10), 69 (10).

(2*E*)-Oct-2-en-6-yn-1-ol (180)[202b]



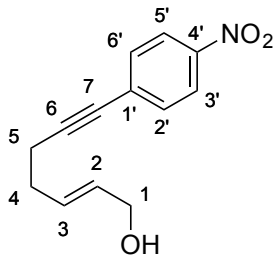
(2*E*)-Oct-2-en-6-yn-1-ol (**180**) was synthesised as described for (2*E*)-hept-2-en-6-yn-1-ol (**179**) using ethyl (2*E*)-oct-2-en-6-ynoate (**175**) (0.558 g, 3.36 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 1:1) gave (2*E*)-oct-2-en-6-yn-1-ol (**180**) (0.363 g, 87%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3337 (OH), 2919 (CH), 1436, 1082, 1000, 968; δ_H (500 MHz, $CDCl_3$) 1.24–1.29 (1H, m, OH), 1.78 (3H, t, *J* 2.4 Hz, 8-H_3), 2.18–2.27 (4H, m, 4-H_2 and 5-H_2), 4.11 (2H, t, *J* 5.3 Hz, 1-H_2), 5.66–5.79 (2H, m, 2-H and 3-H); δ_C (126 MHz, $CDCl_3$) 3.4 (CH_3), 18.8 (CH_2), 31.7 (CH_2), 63.5 (CH_2), 76.0 (C), 78.5 (C), 130.1 (CH), 131.3 (CH); *m/z* (ESI) 147.0782 (MNa^+. $C_8H_{12}NaO$ requires 147.0780), 135 (13%), 91 (22).

(2*E*)-7-Phenylhept-2-en-6-yn-1-ol (181)[101]



(2*E*)-7-Phenylhept-2-en-6-yn-1-ol (**181**) was synthesised as described for (2*E*)-hept-2-en-6-yn-1-ol (**179**) using ethyl (2*E*)-7-phenylhept-2-en-6-ynoate (**176**) (0.670 g, 3.00 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 13:7) gave (2*E*)-7-phenylhept-2-en-6-yn-1-ol (**181**) (0.545 g, 98%) as a colourless oil. Spectroscopic data was consistent with the literature.[101] δ_H (400 MHz, $CDCl_3$) 1.29 (1H, br s, OH), 2.33–2.40 (2H, m, 4-H_2), 2.50 (2H, t, *J* 6.8 Hz, 5-H_2), 4.13 (2H, br s, 1-H_2), 5.72–5.87 (2H, m, 2-H and 3-H), 7.25–7.32 (3H, m, 3 × ArH), 7.36–7.42 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 19.5 (CH_2), 31.5 (CH_2), 63.5 (CH_2), 81.2 (C), 89.4 (C), 123.9 (C), 127.7 (CH), 128.2 (2 × CH), 130.5 (CH), 130.9 (CH), 131.6 (2 × CH); *m/z* (EI) 186 (M^+. 13%), 167 (12), 155 (11), 142 (16), 128 (9), 115 (100), 105 (10), 84 (14).

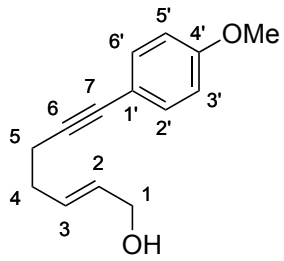
(2*E*)-7-(4'-Nitrophenyl)hept-2-en-6-yn-1-ol (182)



(2*E*)-7-(4'-Nitrophenyl)hept-2-en-6-yn-1-ol (**182**) was synthesised as described for (2*E*)-hept-2-en-6-yn-1-ol (**179**) using ethyl (2*E*)-7-(4'-nitrophenyl)hept-2-en-6-ynoate (**177**) (0.670 g, 2.45 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 6:4) gave (2*E*)-7-(4'-nitrophenyl)hept-2-en-6-yn-1-ol (**182**) (0.469 g, 83%) as a dark green solid. Mp 64–66 ºC; ν_{max}/cm^{-1} (neat) 3374 (OH), 2924 (CH), 1593 (C=C), 1516, 1341, 855, 750; δ_H (400 MHz, $CDCl_3$) 1.35 (1H, br s, OH), 2.35–2.42 (2H, m, 4-H_2), 2.54 (2H, t, *J* 7.1 Hz, 5-H_2), 4.14 (2H, d, *J* 3.2 Hz, 1-H_2), 5.72–5.85 (2H, m, 2-H and 3-H), 7.49–7.54 (2H, m, 2'-H and 6'-H),

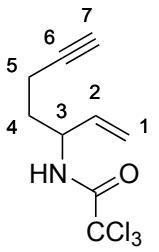
8.13–8.18 (2H, m, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 19.6 (CH_2), 31.1 (CH_2), 63.5 (CH_2), 79.8 (C), 95.6 (C), 123.5 (2 × CH), 130.4 (CH), 130.8 (CH), 130.9 (C), 132.3 (2 × CH), 146.7 (C); *m/z* (ESI) 254.0784 (MNa^+. $C_{13}H_{13}NNaO_3$ requires 254.0788), 227 (9%), 199 (9).

(2*E*)-7-(4'-Methoxyphenyl)hept-2-en-6-yn-1-ol (183)



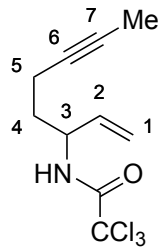
(2*E*)-7-(4-Methoxyphenyl)hept-2-en-6-yn-1-ol (**183**) was synthesised as described for (2*E*)-hept-2-en-6-yn-1-ol (**179**) using ethyl (2*E*)-7-(4'-methoxyphenyl)hept-2-en-6-ynoate (**178**) (0.435 g, 1.68 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 1:1) gave (2*E*)-7-(4'-methoxyphenyl)hept-2-en-6-yn-1-ol (**183**) (0.340 g, 94%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3368 (OH), 2916 (CH), 1607 (C=C), 1508, 1244, 831; δ_H (400 MHz, $CDCl_3$) 1.43 (1H, br s, OH), 2.30–2.41 (2H, m, 4-H_2), 2.47 (2H, t, *J* 7.1 Hz, 5-H_2), 3.79 (3H, s, OCH_3), 4.12 (2H, d, *J* 4.5 Hz, 1-H_2), 5.69–5.85 (2H, m, 2-H and 3-H), 6.78–6.83 (2H, m, 3'-H and 5'-H), 7.29–7.34 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 19.5 (CH_2), 31.6 (CH_2), 55.2 (CH_3), 63.2 (CH_2), 80.9 (C), 87.9 (C), 113.9 (2 × CH), 116.0 (C), 130.4 (CH), 130.7 (CH), 132.9 (2 × CH), 159.1 (C); *m/z* (EI) 216.1153 (M^+. $C_{14}H_{16}O_2$ requires 216.1150), 172 (17%), 145 (100), 130 (7), 102 (15).

3-(2',2',2'-Trichloromethylcarbonylamino)hept-1-en-6-yne (184)[101]



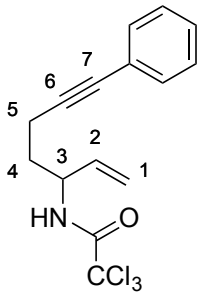
(2*E*)-Hept-2-en-6-yn-1-ol (**179**) (0.110 g, 1.00 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0300 mL, 0.200 mmol) and trichloroacetonitrile (0.150 mL, 1.50 mmol). The reaction mixture was allowed to warm to room temperature before stirring for 3 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in toluene (21 mL) under an argon atmosphere. Bis(acetonitrile)palladium chloride (0.0260 g, 0.100 mmol) was then added to the solution and the reaction mixture was stirred at 40 °C for 24 h. To the reaction mixture, an additional portion of bis(acetonitrile)palladium chloride (0.0260 g, 0.100 mmol) was added and the reaction was stirred at 40 °C for 24 h and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether 10:1) gave 3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**184**) (0.086 g, 34%) as a white solid. Mp 35–37 °C; Spectroscopic data was consistent with the literature.[101] δ_H (500 MHz, $CDCl_3$) 1.84–2.00 (2H, m, 4-H_2), 2.05 (1H, t, *J* 2.7 Hz, 7-H), 2.26–2.39 (2H, m, 5-H_2), 4.56–4.63 (1H, m, 3-H), 5.27 (1H, d, *J* 10.5 Hz, 1-*H*H), 5.30 (1H, d, *J* 17.2 Hz, 1-H*H*), 5.82 (1H, ddd, *J* 17.2, 10.5, 5.6 Hz, 2-H), 6.93 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 14.8 (CH_2), 32.5 (CH_2), 53.0 (CH), 69.9 (CH), 83.1 (C), 92.7 (C), 116.9 (CH_2), 135.4 (CH), 161.3 (C); *m/z* (CI) 254 (MH^+. 72%), 220 (55), 186 (42), 184 (37), 132 (12), 89 (100), 69 (27).

3-(2',2',2'-Trichloromethylcarbonylamino)oct-1-en-6-yne (185)



3-(2',2',2'-Trichloromethylcarbonylamino)oct-1-en-6-yne (**185**) was synthesised as described for 3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**184**), except using (2*E*)-oct-2-en-6-yn-1-ol (**180**) (0.040 g, 0.34 mmol) and a single portion of bis(acetonitrile)palladium chloride (0.0090 g, 0.034 mmol). The reaction was performed at 20 °C for 24 h. Purification by flash column chromatography (petroleum ether/diethyl ether, 7:3) gave 3-(2',2',2'-trichloromethylcarbonylamino)oct-1-en-6-yne (**185**) (0.050 g, 55%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3331 (NH), 2920 (CH), 1694 (C=O), 1516 (C=C), 1441, 1250, 926, 822; δ_H (400 MHz, $CDCl_3$) 1.73–1.95 (5H, m, 4-H_2 and 8-H_3), 2.20–2.30 (2H, m, 5-H_2), 4.51–4.62 (1H, m, 3-H), 5.19–5.30 (2H, m, 1-H_2), 5.79 (1H, ddd, *J* 17.2, 10.4, 5.4 Hz, 2-H), 7.14 (1H, d, *J* 5.4 Hz, NH); δ_C (101 MHz, $CDCl_3$) 3.7 (CH_3), 14.9 (CH_2), 32.7 (CH_2), 53.2 (CH), 77.3 (C), 78.0 (C), 92.8 (C), 116.4 (CH_2), 135.6 (CH), 161.2 (C); *m/z* (ESI) 289.9865 (MNa^+. $C_{10}H_{12}{}^{35}Cl_3NNaO$ requires 289.9877).

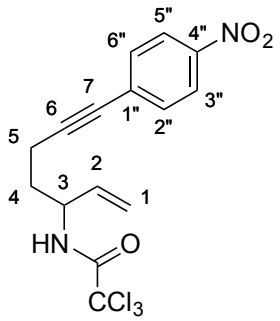
7-Phenyl-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (186)



7-Phenyl-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**186**) was synthesised as described for 3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**184**), except using (2*E*)-7-phenylhept-2-en-6-yn-1-ol (**181**) (0.080 g, 0.44 mmol) and a single portion of bis(acetonitrile)palladium chloride (0.012 g, 0.044 mmol). The reaction was performed at 20 °C for 12 h. Flash column

chromatography (petroleum ether/diethyl ether, 1:1) gave 7-phenyl-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**186**) (0.12 g, 81%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3304 (NH), 2955 (CH), 2362, 1714 (C=O), 1511, 1265, 1175; δ_H (400 MHz, $CDCl_3$) 1.90–2.09 (2H, m, 4-H_2), 2.48–2.61 (2H, m, 5-H_2), 4.60–4.69 (1H, m, 3-H), 5.27 (1H, d, *J* 10.4 Hz, 1-*H*H), 5.32 (1H, d, *J* 17.2 Hz, 1-H*H*), 5.85 (1H, ddd, *J* 17.2, 10.4, 5.6 Hz, 2-H), 6.98 (1H, d, *J* 7.4 Hz, NH), 7.26–7.32 (3H, m, 3 × ArH), 7.37–7.44 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 15.9 (CH_2), 32.8 (CH_2), 53.2 (CH), 82.0 (C), 88.4 (C), 92.7 (C), 116.9 (CH_2), 123.4 (C), 128.0 (CH), 128.3 (2 × CH), 131.7 (2 × CH), 135.6 (CH), 161.4 (C); *m/z* (ESI) 352.0019 (MNa^+. $C_{15}H_{14}{}^{35}Cl_3NNaO$ requires 352.0033).

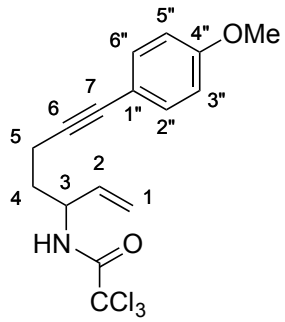
7-(4''-Nitrophenyl)-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (187)



7-(4''-Nitrophenyl)-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**187**) was synthesised as described for 3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**184**), except using (2*E*)-7-(4'-nitrophenyl)hept-2-en-6-yn-1-ol (**182**) (0.060 g, 0.26 mmol) and a single portion of bis(acetonitrile)palladium chloride (0.0080 g, 0.026 mmol). The reaction was performed at 20 °C for 12 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave 7-(4''-nitrophenyl)-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**187**) (0.074 g, 76%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3339 (NH), 2932 (CH), 1697 (C=O), 1514 (C=C), 1341, 1107, 852, 820; δ_H (400 MHz, $CDCl_3$) 1.93–2.08 (2H, m, 4-H_2), 2.50–2.64 (2H, m, 5-H_2), 4.58–4.68 (1H, m, 3-H), 5.25–5.36 (2H, m, 1-H_2), 5.85 (1H, ddd, *J* 17.2, 10.4, 5.7 Hz, 2-H), 6.80 (1H, d, *J* 7.9 Hz, NH), 7.50–7.55 (2H, m, 2''-H and 6''-H), 8.12–8.17 (2H, m, 3''-H and 5''-H); δ_C (101 MHz, $CDCl_3$) 16.2 (CH_2), 32.7 (CH_2), 53.0 (CH), 80.4 (C), 92.7 (C), 94.3 (C), 117.2 (CH_2), 123.5 (2 × CH),

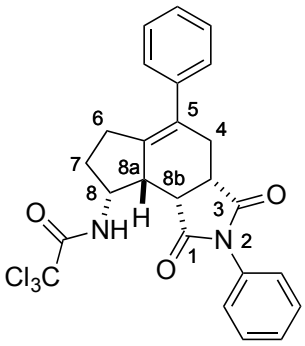
130.5 (C), 132.4 (2 × CH), 135.5 (CH), 146.8 (C), 161.4 (C); *m/z* (ESI) 396.9873 (MNa^+. $C_{15}H_{13}{}^{35}Cl_3N_2NaO_3$ requires 396.9884).

7-(4”-Methoxyphenyl)-3-(2’,2’,2’-trichloromethylcarbonylamino)hept-1-en-6-yne (188)



7-(4”-Methoxyphenyl)-3-(2’,2’,2’-trichloromethylcarbonylamino)hept-1-en-6-yne (**188**) was synthesised as described for 3-(2’,2’,2’-trichloromethylcarbonylamino)hept-1-en-6-yne (**184**), except using (2*E*)-7-(4**’**-methoxyphenyl)hept-2-en-6-yn-1-ol (**183**) (0.11 g, 0.49 mmol) and a single portion of bis(acetonitrile)palladium chloride (0.014 g, 0.049 mmol). The reaction was performed at 20 °C for 12 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave 7-(4”-methoxyphenyl)-3-(2’,2’,2’-trichloromethylcarbonylamino)hept-1-en-6-yne (**188**) (0.15 g, 83%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3340 (NH), 2925 (CH), 1697 (C=O), 1509 (C=C), 1246, 1173, 831; δ_H (400 MHz, $CDCl_3$) 1.89–2.08 (2H, m, 4-H_2), 2.45–2.62 (2H, m, 5-H_2), 3.80 (3H, s, OCH_3), 4.59–4.69 (1H, m, 3-H), 5.24–5.35 (2H, m, 1-H_2), 5.85 (1H, ddd, *J* 17.1, 10.4, 5.5 Hz, 2-H), 6.79–6.84 (2H, m, 3”-H and 5”-H), 7.02 (1H, d, *J* 8.0 Hz, NH), 7.30–7.36 (2H, m, 2”-H and 6”-H); δ_C (126 MHz, $CDCl_3$) 15.8 (CH_2), 32.8 (CH_2), 53.2 (CH), 55.3 (CH_3), 81.9 (C), 86.8 (C), 92.7 (C), 113.9 (2 × CH), 115.4 (C), 116.7 (CH_2), 133.0 (2 × CH), 135.6 (CH), 159.3 (C), 161.4 (C); *m/z* (ESI) 382.0120 (MNa^+. $C_{16}H_{16}{}^{35}Cl_3NNaO_2$ requires 382.0139).

(3a*S,8*R**,8a*S**,8b*R**)-2,5-Diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (201)[101]**

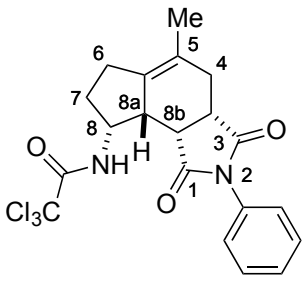


Method A- (2*E*)-7-Phenylhept-2-en-6-yn-1-ol (**181**) (0.120 g, 0.640 mmol) was dissolved in dichloromethane (16 mL) and cooled to 0 °C. To the solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0200 mL, 0.0130 mmol) and trichloroacetonitrile (0.100 mL, 0.966 mmol) were added. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was filtered through a short pad of silica gel with diethyl ether (300 mL) and the filtrate concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in toluene (16 mL) and bis(acetonitrile)palladium chloride (0.0180 g, 0.0640 mmol) was then added and the reaction mixture was stirred at room temperature for 12 h. Grubbs second generation catalyst (0.0400 g, 0.0500 mmol) was added with 1,7-octadiene (0.390 mL, 2.58 mmol) and the reaction mixture was stirred for 18 h at 90 °C. *N*-Phenyl maleimide (0.170 g, 0.960 mmol) was added with hydroquinone (0.008 g, 0.080 mmol). The reaction mixture was stirred for 18 h at 75 °C. The reaction mixture was then cooled and the solvent was evaporated. Flash column chromatography (petroleum ether/diethyl ether, 7:3) gave (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (0.166 g, 51%) as a yellow solid. Mp 151–153 °C; Spectroscopic data was consistent with the literature.[101] δ_H (400 MHz, $CDCl_3$) 1.75 (1H, dq, *J* 12.3, 10.2 Hz, 7-*H*H), 2.10–2.20 (1H, m, 7-H*H*), 2.53–2.66 (3H, m, 4-*H*H and 6-H_2), 3.12 (1H, dd, *J* 9.1, 5.8 Hz, 8a-H), 3.30 (1H, dd, *J* 15.2, 1.4 Hz, 4-H*H*), 3.46–3.56 (2H, m, 3a-H and 8b-H), 4.88–5.01 (1H, m, 8-H), 7.06–7.10 (2H, m, 2 × ArH), 7.23–7.47

(8H, m, 8 × ArH), 8.96 (1H, d, *J* 9.6 Hz, NH); δ_C (126 MHz, $CDCl_3$) 28.4 (CH_2), 29.9 (CH_2), 31.6 (CH_2), 40.3 (CH), 41.7 (CH), 43.7 (CH), 52.8 (CH), 92.9 (C), 126.5 (2 × CH), 127.2 (CH), 127.5 (2 × CH), 128.5 (2 × CH), 129.2 (CH), 129.4 (2 × CH), 130.3 (C), 131.4 (C), 139.0 (C), 139.6 (C), 162.3 (C), 178.5 (C), 179.7 (C); *m/z* (ESI) 525 (MNa^+. 100%), 481 (18), 454 (7), 413 (7), 345 (24), 323 (21), 297 (9), 236 (11), 218 (7).

Method B- To a solution of (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-iodo-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**240**) (0.025 g, 0.045 mmol) in a 5:1 mixture of toluene/methanol (3 mL) at room temperature was added phenylboronic acid (0.0080 g, 0.070 mmol), tetrakis(triphenylphosphine)palladium(0) (0.0050 g, 0.0050 mmol) and potassium carbonate (0.025 g, 0.18 mmol). The reaction mixture was heated to 70 °C and stirred for 48 h. The mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (5 mL), washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether, 7:3) gave (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (0.017 g, 76%) as a yellow solid. Spectroscopic data was as described above.

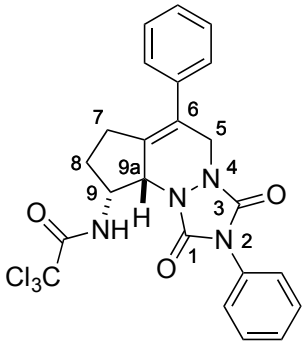
(3a*S,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-Hexahydro-5-methyl-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (202)**



(3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-Hexahydro-5-methyl-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**202**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-

hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method A) using (2*E*)-oct-2-en-6-yn-1-ol (**180**) (0.050 g, 0.36 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 7:3) gave (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-methyl-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**202**) (0.040 g, 25%) as a white solid. Mp 126–128 °C; ν_{max}/cm^{-1} (neat) 3303 (NH), 2928 (CH), 1696 (C=O), 1518 (C=C), 1389, 1188, 736; δ_H (400 MHz, $CDCl_3$) 1.69–1.81 (4H, m, 7-*H*H and 5-CH_3), 2.09–2.22 (2H, m, 6-*H*H and 7-H*H*), 2.26–2.35 (1H, m, 4-*H*H), 2.45–2.55 (1H, m, 6-H*H*), 2.69 (1H, dd, *J* 14.8, 1.4 Hz, 4-H*H*), 2.84–2.91 (1H, m, 8a-H), 3.31 (1H, ddd, *J* 8.6, 7.1, 1.4 Hz, 3a-H), 3.38 (1H, dd, *J* 8.6, 6.2 Hz, 8b-H), 4.76–4.89 (1H, m, 8-H), 7.11–7.15 (2H, m, 2 × ArH), 7.38–7.50 (3H, m, 3 × ArH), 8.97 (1H, d, *J* 9.6 Hz, NH); δ_C (101 MHz, $CDCl_3$) 19.3 (CH_3), 26.1 (CH_2), 31.6 (CH_2), 31.9 (CH_2), 39.9 (CH), 41.4 (CH), 42.5 (CH), 53.1 (CH), 92.9 (C), 126.2 (C), 126.4 (2 × CH), 129.1 (CH), 129.3 (2 × CH), 131.6 (C), 136.3 (C), 162.2 (C), 178.5 (C), 179.9 (C); *m/z* (ESI) 463.0350 (MNa^+. $C_{20}H_{19}{}^{35}Cl_3N_2NaO_3$ requires 463.0353).

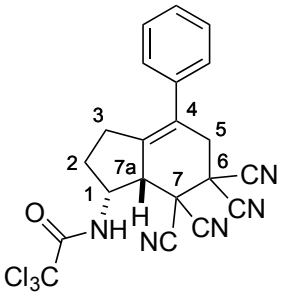
(9*R,9a*S**)-2,6-Diphenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (203)**



(9*R**,9a*S**)-2,6-Diphenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-a]pyridazine-1,3(2H)-dione (**203**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method A) using (2*E*)-7-phenylhept-2-en-6-yn-1-ol (**181**) (0.080 g, 0.40 mmol) and

4-phenyl-1,2,4-triazole-3,5-dione (0.13 g, 0.72 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave (9*R**,9a*S**)-2,6-diphenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (**203**) (0.080 g, 40%) as a dark yellow solid. Mp 176–178 °C; ν_{max}/cm^{-1} (neat) 3405 (NH), 2925 (CH), 1714 (C=O), 1704 (C=O) 1503 (C=C), 1420, 752; δ_H (400 MHz, $CDCl_3$) 2.14–2.29 (2H, m, 8-H_2), 2.44– 2.54 (1H, m, 7-*H*H), 2.60–2.71 (1H, m, 7-H*H*), 4.40 (1H, ddd, *J* 16.6, 5.3, 2.3 Hz, 5-*H*H), 4.54 (1H, ddd, *J* 16.6, 5.3, 2.9 Hz, 5-H*H*), 4.57–4.61 (1H, m, 9a-H), 4.90–4.95 (1H, m, 9-H), 6.73 (1H, d, *J* 6.0 Hz, NH), 7.28–7.56 (10H, m, 10 × ArH); δ_C (101 MHz, $CDCl_3$) 24.4 (CH_2), 27.8 (CH_2), 45.6 (CH_2), 52.5 (CH), 59.9 (CH), 92.7 (C), 125.5 (2 × CH), 127.7 (2 × CH), 128.4 (CH), 128.7 (CH), 128.7 (C), 128.9 (2 × CH), 129.2 (2 × CH), 130.9 (C), 132.3 (C), 136.3 (C), 151.7 (C), 152.7 (C), 161.3 (C); *m/z* (ESI) 527.0395 (MNa^+. $C_{23}H_{19}{}^{35}Cl_3N_4NaO_3$ requires 527.0415).

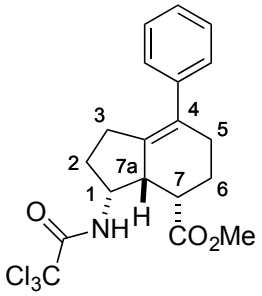
(1*R,7a*R**)-2,3,5,6,7,7a-Hexahydro-4-phenyl-6,6,7,7-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)indene (204)**



(1*R**,7a*R**)-2,3,5,6,7,7a-Hexahydro-4-phenyl-6,6,7,7-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)indene (**204**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method A) using (2*E*)-7-phenylhept-2-en-6-yn-1-ol (**181**) (0.0600 g, 0.320 mmol) and tetracyanoethylene (0.250 g, 1.93 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 10:1) gave (1*R**,7a*R**)-2,3,5,6,7,7a-hexahydro-4-phenyl-6,6,7,7-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)indene (**204**) (0.083 g, 56%) as a yellow solid. Mp 136–138 °C; ν_{max}/cm^{-1} (neat) 3347 (NH), 2927 (CH), 1705 (C=O), 1517 (C=C),

1218, 823, 769; δ_H (400 MHz, $CDCl_3$) 1.90–2.03 (1H, m, 2-*H*H), 2.33–2.47 (2H, m, 2-H*H* and 3-*H*H), 2.63–2.74 (1H, m, 3-H*H*), 3.31 (1H, dt, *J* 16.4, 1.7 Hz, 5-*H*H), 3.46–3.56 (2H, m, 5-H*H* and 7a-H), 4.41–4.53 (1H, m, 1-H), 6.92 (1H, *J* 7.6 Hz, NH), 7.17–7.22 (2H, m, 2 × ArH), 7.35–7.47 (3H, m, 3 × ArH); δ_C (126 MHz, $CDCl_3$) 26.3 (CH_2), 29.0 (CH_2), 37.5 (CH_2), 39.7 (C), 41.4 (C), 49.7 (CH), 54.9 (CH), 91.8 (C), 108.2 (C), 110.5 (C), 110.8 (C), 110.8 (C), 127.1 (2 × CH), 127.8 (C), 129.0 (CH), 129.2 (2 × CH), 131.4 (C), 136.4 (C), 162.5 (C); *m/z* (ESI) 480.0133 (MNa^+. $C_{21}H_{14}{}^{35}Cl_3N_5NaO$ requires 480.0156).

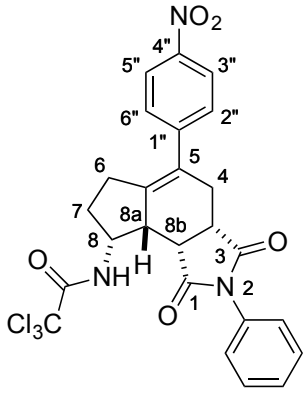
Methyl (1*R,7*S**,7a*S**)-2,3,5,6,7,7a-hexahydro-4-phenyl-1-(2',2',2'-trichloromethylcarbonylamino)indene-7-carboxylate** (**205**)



Methyl (1*R**,7*S**,7a*S**)-2,3,5,6,7,7a-hexahydro-4-phenyl-1-(2',2',2'-trichloromethylcarbonylamino)indene-7-carboxylate (**205**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method A) using (2*E*)-7-phenylhept-2-en-6-yn-1-ol (**181**) (0.0900 g, 0.480 mmol) and methyl acrylate (0.130 mL, 1.44 mmol). The Diels-Alder reaction was stirred for 5 days at 111 °C. Purification by flash column chromatography (petroleum ether/diethyl ether, 8:2) gave methyl (1*R**,7*S**,7a*S**)-2,3,5,6,7,7a-hexahydro-4-phenyl-1-(2',2',2'-trichloromethylcarbonylamino)indene-7-carboxylate (**205**) (0.090 g, 46%) as a yellow oil; ν_{max}/cm^{-1} (neat) 3414 (NH), 2952 (CH), 1712 (C=O), 1511 (C=C), 1200, 822, 757; δ_H (500 MHz, $CDCl_3$) 1.65–1.77 (1H, m, 2-*H*H), 1.95–2.10 (2H, m, 2-H*H* and 6-*H*H), 2.22–2.38 (3H, m, 3-*H*H, 5-*H*H and 6-H*H*), 2.40–2.49 (1H, m, 3-H*H*), 2.50–2.62 (1H, m, 5-H*H*), 3.00 (1H, q, *J* 4.5 Hz, 7-H), 3.04–3.12 (1H, m, 7a-H), 3.72 (1H, s, OCH_3), 4.63 (1H, qd, *J* 8.6, 5.0 Hz, 1-H), 7.16–7.26 (3H, m, 3 × ArH), 7.29–7.36 (2H, m, 2 × ArH), 7.68 (1H, d, *J* 8.6 Hz, NH); δ_C (126 MHz, $CDCl_3$) 26.4 (CH_2), 27.8 (CH_2), 28.9 (CH_2), 31.7 (CH_2), 39.5

(CH), 43.9 (CH), 52.1 (CH), 53.2 (CH_3), 92.9 (C), 126.6 (CH), 127.6 (2 × CH), 128.1 (2 × CH), 130.0 (C), 136.0 (C), 141.9 (C), 161.7 (C), 175.5 (C); *m/z* (ESI) 438.0381 (MNa^+. $C_{19}H_{20}{}^{35}Cl_3NNaO_3$ requires 438.0401).

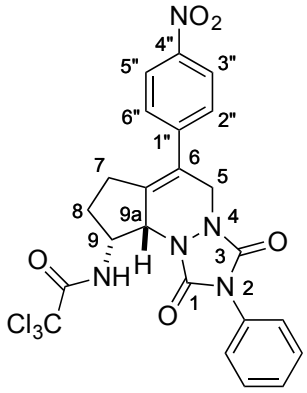
(3a*S,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-Hexahydro-5-(4”-nitrophenyl)-2-phenyl-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (206)**



(3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-Hexahydro-5-(4”-nitrophenyl)-2-phenyl-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**206**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method A) using (2*E*)-7-(4’-nitrophenyl)hept-2-en-6-yn-1-ol (**182**) (0.050 g, 0.20 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-(4”-nitrophenyl)-2-phenyl-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**206**) (0.076 g, 69%) as a yellow solid. Mp 160–162 °C; ν_{max}/cm^{-1} (neat) 3306 (NH), 2956 (CH), 1695 (C=O), 1513 (C=C), 1344, 1191, 821, 753; δ_H (400 MHz, $CDCl_3$) 1.79 (1H, qd, *J* 12.4, 8.0 Hz, 7-*H*H), 2.16–2.26 (1H, m, 7-H*H*), 2.50–2.70 (3H, m, 4-*H*H and 6-H_2), 3.17 (1H, dd, *J* 9.5, 6.1 Hz, 8a-H), 3.33 (1H, dd, *J* 14.8, 1.0 Hz, 4-H*H*), 3.53–3.59 (2H, m, 3a-H and 8b-H), 4.90–5.02 (1H, m, 8-H), 7.02–7.08 (2H, m, 2”-H and 6”-H), 7.37–7.49 (5H, m, 5 × ArH), 8.16–8.27 (2H, m, 3”-H and 5”-H), 8.93 (1H, d, *J* 9.5 Hz, NH); δ_C (126 MHz, $CDCl_3$) 28.6 (CH_2), 31.3 (CH_2), 31.7 (CH_2), 40.2 (CH), 41.4 (CH), 44.2 (CH), 52.6 (CH), 92.8 (C), 123.8 (2 × CH), 126.4

(2 × CH), 128.2 (2 × CH), 128.9 (C), 129.4 (CH), 129.5 (2 × CH), 131.2 (C), 143.7 (C), 145.4 (C), 146.7 (C), 162.4 (C), 178.3 (C), 179.3 (C); *m/z* (ESI) 570.0347 (MNa^+. $C_{25}H_{20}{}^{35}Cl_3N_3NaO_5$ requires 570.0361).

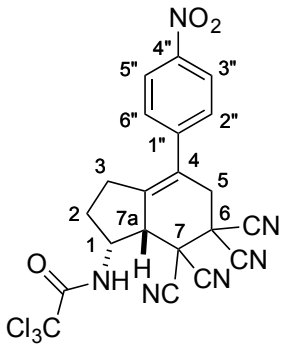
(9*R,9a*S**)-6-(4''-Nitrophenyl)-2-phenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (207)**



(9*R**,9a*S**)-6-(4''-Nitrophenyl)-2-phenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (**207**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method A) using (2*E*)-7-(4'-nitrophenyl)hept-2-en-6-yn-1-ol (**182**) (0.070 g, 0.30 mmol) and 4-phenyl-1,2,4-triazole-3,5-dione (0.060 g, 0.36 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave (9*R**,9a*S**)-6-(4''-nitrophenyl)-2-phenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (**207**) (0.11 g, 63%) as a yellow solid. Mp 160–162 °C; ν_{max}/cm^{-1} (neat) 3398 (NH), 2925 (CH), 1711 (C=O), 1515 (C=C), 1420, 1343, 854, 751; δ_H (400 MHz, $CDCl_3$) 2.22–2.33 (2H, m, 8-H_2), 2.45–2.56 (1H, m, 7-*H*H), 2.60–2.72 (1H, m, 7-H*H*), 4.41 (1H, dq, *J* 16.0, 4.0 Hz, 5-*H*H), 4.52 (1H, dq, *J* 16.0, 4.0 Hz, 5-H*H*), 4.57–4.62 (1H, m, 9a-H), 4.86–4.93 (1H, m, 9-H), 6.77 (1H, d, *J* 5.8 Hz, NH), 7.33–7.54 (7H, m, 7 × ArH), 8.24–8.31 (2H, m, 3''-H and 5''-H); δ_C (101 MHz, $CDCl_3$) 24.9 (CH_2), 27.6 (CH_2), 45.3 (CH_2), 52.6 (CH), 60.4 (CH), 92.6 (C), 124.2 (2 × CH), 125.5 (2 × CH), 126.5 (C), 128.6 (CH), 128.7 (2 × CH), 129.3 (2 × CH),

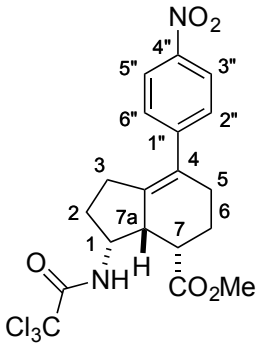
130.7 (C), 136.0 (C), 142.9 (C), 147.6 (C), 151.8 (C), 152.8 (C), 161.5 (C); *m/z* (ESI) 572.0239 (MNa^+. $C_{23}H_{18}{}^{35}Cl_3N_5NaO_5$ requires 572.0266).

(1*R,7a*R**)-2,3,5,6,7,7a-Hexahydro-4-(4”-nitrophenyl-6,6,7,7-tetracyano-1-(2’,2’,2’- trichloromethylcarbonylamino)indene (208)**



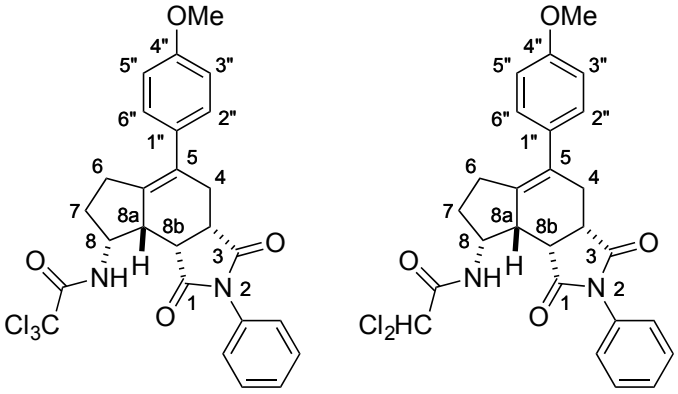
(1*R**,7a*R**)-2,3,5,6,7,7a-Hexahydro-4-(4”-nitrophenyl-6,6,7,7-tetracyano-1-(2’,2’,2’-trichloromethylcarbonylamino)indene (**208**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method A) using (2*E*)-7-(4’-nitrophenyl)hept-2-en-6-yn-1-ol (**182**) (0.070 g, 0.30 mmol) and tetracyanoethylene (0.23 g, 1.8 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 6:4) gave (1*R**,7a*R**)-2,3,5,6,7,7a-hexahydro-4-(4”-nitrophenyl-6,6,7,7-tetracyano-1-(2’,2’,2’-trichloromethylcarbonylamino)indene (**208**) (0.11 g, 73%) as a yellow solid. Mp 128–130 °C; ν_{max}/cm^{-1} (neat) 3334 (NH), 2924 (CH), 1709 (C=O), 1520 (C=C), 1347, 1218, 855, 757; δ_H (400 MHz, $CDCl_3$) 1.98–2.09 (1H, m, 2-*H*H), 2.31–2.46 (2H, m, 2-H*H* and 3-*H*H), 2.65–2.74 (1H, m, 3-H*H*), 3.29–3.37 (1H, m, 5-*H*H), 3.50–3.58 (2H, m, 5-H*H* and 7a-H), 4.43–4.52 (1H, m, 1-H), 6.95 (1H, d, *J* 8.3 Hz, NH), 7.39–7.44 (2H, m, 2”-H and 6”-H), 8.29–8.34 (2H, m, 3”-H and 5”-H); δ_C (101 MHz, $CDCl_3$) 26.4 (CH_2), 28.8 (CH_2), 37.0 (CH_2), 39.6 (C), 41.3 (C), 49.8 (CH), 54.8 (CH), 91.7 (C), 108.1 (C), 110.2 (C), 110.5 (C), 110.5 (C), 124.5 (2 × CH), 126.0 (C), 128.6 (2 × CH), 134.0 (C), 142.8 (C), 148.0 (C), 162.7 (C); *m/z* (ESI) 524.9983 (MNa^+. $C_{21}H_{13}{}^{35}Cl_3N_6NaO_3$ requires 525.0007), 357 (21%), 303 (22), 289 (29), 253 (25), 235 (8).

Methyl (1*R,7*S**,7a*S**)-2,3,5,6,7,7a-hexahydro-4-(4”-nitrophenyl)-1-(2’,2’,2’-trichloromethylcarbonylamino)indene-7-carboxylate (209)**



Methyl (1*R**,7*S**,7a*S**)-2,3,5,6,7,7a-hexahydro-4-(4”-nitrophenyl)-1-(2’,2’,2’-trichloromethylcarbonylamino)indene-7-carboxylate (**209**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method A) using (2*E*)-7-(4’-nitrophenyl)hept-2-en-6-yn-1-ol (**182**) (0.070 g, 0.29 mmol) and methyl acrylate (0.080 mL, 0.87 mmol). The Diels-Alder reaction was stirred for 5 days at 111 °C. Purification by flash column chromatography (petroleum ether/diethyl ether, 8:2) gave methyl (1*R**,7*S**,7a*S**)-2,3,5,6,7,7a-hexahydro-4-(4”-nitrophenyl)-1-(2’,2’,2’- trichloromethylcarbonylamino)indene-7-carboxylate (**209**) (0.062 g, 46%) as a colourless oil; ν_{max}/cm^{-1} (neat) 3389 (NH), 2930 (CH), 1710 (C=O), 1514 (C=C), 1344, 821, 752; δ_H (400 MHz, $CDCl_3$) 1.71–1.84 (1H, m, 2-*H*H), 1.95–2.15 (2H, m, 2-H*H* and 3-*H*H), 2.24–2.61 (5H, m, 3-H*H*, 5-H_2 and 6-H_2), 3.04 (1H, q, *J* 4.2 Hz, 7-H), 3.09–3.15 (1H, m, 7a-H), 3.72 (1H, s, OCH_3), 4.66 (1H, qd, *J* 9.0, 7.2 Hz, 1-H), 7.32–7.38 (2H, m, 2”-H and 6”-H), 7.58 (1H, d, *J* 9.0 Hz, NH), 8.16–8.22 (2H, m, 3”-H and 5”-H); δ_C (101 MHz, $CDCl_3$) 26.5 (CH_2), 27.3 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 39.2 (CH), 44.2 (CH), 52.2 (CH), 52.9 (CH_3), 92.7 (C), 123.5 (2 × CH), 127.8 (C), 128.4 (2 × CH), 139.5 (C), 146.4 (C), 148.7 (C), 161.8 (C), 175.5 (C); *m/z* (EI) 460.0359 (M^+. $C_{19}H_{19}{}^{35}Cl_3N_2O_5$ requires 460.0360), 299 (100%), 240 (71), 194 (16), 165 (12), 83 (17).

(3a*S*,8*R***,8a*S***,8b*R***)-3a,4,6,7,8a,8b-Hexahydro-5-(4''-methoxyphenyl)-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (210) and (3a*S***,8*R***,8a*S***,8b*R***)-(4''-methoxyphenyl)-2-phenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2'-dichloromethylcarbonylamino)cyclopent[e]isoindole-1,3(2H,3aH)-dione (210b)**



Method A- (3a*S***,8*R***,8a*S***,8b*R***)-3a,4,6,7,8a,8b-Hexahydro-5-(4''-methoxyphenyl)-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**210**) was synthesised as described for (3a*S***,8*R***,8a*S***,8b*R***)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method A) using (2*E*)-7-(4**'**-methoxyphenyl)hept-2-en-6-yn-1-ol (**183**) (0.065 g, 0.30 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave (3a*S***,8*R***,8a*S***,8b*R***)-3a,4,6,7,8a,8b-hexahydro-5-(4''-methoxyphenyl)-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**210**) (0.054 g, 34%) as a yellow solid. Mp 115–117 °C; ν_{max}/cm^{-1} (neat) 3308 (NH), 2959 (CH), 1698 (C=O), 1512 (C=C), 1391, 1247, 823; δ_H (400 MHz, $CDCl_3$) 1.66–1.81 (1H, m, 7-*H*H), 2.09–2.19 (1H, m, 7-H*H*), 2.52–2.62 (3H, m, 4-*H*H and 6-H_2), 3.10 (1H, dd, *J* 8.9, 6.3 Hz, 8a-H), 3.27 (1H, dd, *J* 15.2, 1.2 Hz, 4-H*H*), 3.44–3.54 (2H, m, 3a-H and 8b-H), 3.81 (3H, s, OCH_3), 4.87–4.99 (1H, m, 8-H), 6.85–6.92 (2H, m, 3''-H and 5''-H), 7.04–7.09 (2H, m, 2 × ArH), 7.17–7.23 (2H, m, 2''-H and 6''-H), 7.34–7.46 (3H, m, 3 × ArH), 8.97 (1H, d, *J* 9.6 Hz, NH); δ_C (101 MHz, $CDCl_3$) 28.3 (CH_2), 31.6 (CH_2), 31.7 (CH_2), 40.3 (CH), 41.7 (CH), 43.7 (CH), 52.9 (CH), 55.3 (CH_3), 92.9 (C), 113.8 (2 × CH), 126.5 (2 × CH), 128.7 (2 × CH), 129.1

(CH), 129.4 (2 × CH), 129.8 (C), 131.4 (C), 131.5 (C), 138.1 (C), 158.7 (C), 162.3 (C), 178.6 (C), 179.8 (C); *m/z* (ESI) 555.0599 (MNa^+. $C_{26}H_{23}{}^{35}Cl_3N_2NaO_4$ requires 555.0616).

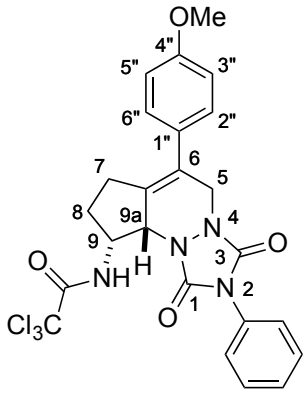
Method B- 7-(4”-Methoxyphenyl)-3-(2’,2’,2’-trichloromethylcarbonylamino)hept-1-en-6-yne (**188**) (0.043 g, 0.12 mmol) was dissolved in toluene (3 mL) and Grubbs second generation catalyst (0.0070 g, 0.0080 mmol) was added with 1,7-octadiene (0.070 mL, 0.48 mmol) and the reaction mixture was stirred for 20 h at 40 °C. *N*-Phenyl maleimide (0.030 g, 0.18 mmol) was added with hydroquinone (0.003 g, 0.030 mmol). The reaction mixture was stirred for 24 h at 75 °C. The reaction mixture was then cooled and the solvent was evaporated. Purification by flash column chromatography (petroleum ether/diethyl ether, 8:2) gave (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-(4”-methoxyphenyl)-2-phenyl-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**210**) (0.042 g, 65%) as a yellow solid. Spectroscopic data was as described above.

Method C- (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-Hexahydro-5-(4”-methoxyphenyl)-2-phenyl-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**210**) was synthesised as described for 3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method B) using (3aS*,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-iodo-2-phenyl-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**240**) (0.025 g, 0.045 mmol) and 4-methoxyphenylboronic acid (0.010 g, 0.070 mmol) and performed at 70 °C for 36 h. Flash column chromatography (petroleum ether/diethyl ether, 8:2) gave (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-(4”-methoxyphenyl)-2-phenyl-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**210**) (0.013 g, 53%) as a yellow solid. Spectroscopic data was as described above.

Further elution (petroleum ether/diethyl ether 6:4) gave (3a*S**,8*R**,8a*S**,8b*R**)-(4”-methoxyphenyl)-2-phenyl-3a,4,6,7,8a,8b-hexahydro-8-(2′,2′-

dichloromethylcarbonylamino)cyclopent[e]isoindole-1,3(2H,3aH)-dione (**210b**) (2.4 mg, 10%) as a white solid. Mp 110–112 °C; ν_{max}/cm^{-1} (neat) 3334 (NH), 2935 (CH), 1702 (C=O), 1513 (C=C), 1391, 1249, 1181, 909, 773, 732; δ_H (400 MHz, $CDCl_3$) 1.66–1.78 (1H, m, 7-*H*H), 2.06–2.13 (1H, m, 7-H*H*), 2.49–2.61 (3H, m, 4-*H*H and 6-H_2), 3.06 (1H, dd, *J* 8.5, 6.6 Hz, 8a-H), 3.26 (1H, dd, *J* 15.0, 1.1 Hz, 4-H*H*), 3.43–3.54 (2H, m, 3a-H and 8b-H), 3.81 (3H, s, OCH_3), 4.89–4.99 (1H, m, 8-H), 5.98 (1H, s, $CHCl_2$), 6.85–6.91 (2H, m, 3"-H and 5"-H), 7.06–7.10 (2H, m, 2 × ArH), 7.17–7.22 (2H, m, 2"-H and 6"-H), 7.36–7.46 (3H, m, 3 × ArH), 8.66 (1H, d, *J* 9.7 Hz, NH); δ_C (101 MHz, $CDCl_3$) 28.3 (CH_2), 31.6 (CH_2), 31.7 (CH_2), 40.4 (CH), 41.7 (CH), 43.7 (CH), 51.6 (CH), 55.3 (CH_3), 66.7 (CH), 113.8 (2 × CH), 126.6 (2 × CH), 128.7 (2 × CH), 129.1 (CH), 129.3 (2 × CH), 129.6 (C), 131.4 (C), 131.5 (C), 138.3 (C), 158.6 (C), 164.5 (C), 178.7 (C), 179.7 (C); *m/z* (ESI) 521.0982 (MNa^+. $C_{26}H_{24}{}^{35}Cl_2N_2NaO_4$ requires 521.1005).

(9*R,9a*S**)-6-(4"-Methoxyphenyl)-2-phenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (211)**

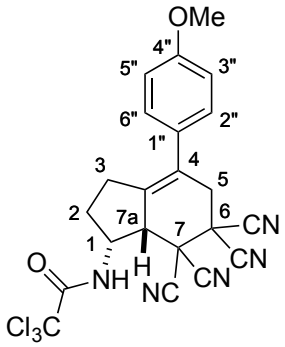


Method A- (9*R**,9a*S**)-6-(4"-Methoxyphenyl)-2-phenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (**211**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method A) using (2*E*)-7-(4**'**-methoxyphenyl)hept-2-en-6-yn-1-ol (**183**) (0.060 g, 0.28 mmol) and 4-phenyl-1,2,4-triazole-3,5-dione (0.059 g, 0.34 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 6:4)

gave (9*R**,9a*S**)-6-(4”-methoxyphenyl)-2-phenyl-7,8,9,9a-tetrahydro-9-(2’,2’,2’-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (**211**) (0.032 g, 23%) as a dark yellow solid. Mp 154–156 °C; ν_{max}/cm^{-1} (neat) 3406 (NH), 2932 (CH), 1774 (C=O), 1715 (C=O), 1703 (C=O), 1510 (C=C), 1420, 1250, 821, 734; δ_H (400 MHz, $CDCl_3$) 2.12–2.30 (2H, m, 8-H_2), 2.44–2.56 (1H, m, 7-*H*H), 2.61–2.71 (1H, m, 7-H*H*), 3.85 (3H, s, OCH_3), 4.36 (1H, ddd, *J* 16.0, 4.8, 2.6 Hz, 5-*H*H), 4.49–4.61 (2H, m, 5-H*H* and 9a-H), 4.92 (1H, q, *J* 5.8 Hz, 9-H), 6.70 (1H, d, *J* 5.8 Hz, NH), 6.93–6.99 (2H, m, 3”-H and 5”-H), 7.22–7.56 (7H, m, 7 × ArH); δ_C (101 MHz, $CDCl_3$) 24.5 (CH_2), 27.9 (CH_2), 45.5 (CH_2), 52.3 (CH), 55.4 (CH_3), 59.8 (CH), 92.6 (C), 114.3 (2 × CH), 125.5 (2 × CH), 128.2 (C), 128.4 (CH), 128.4 (C), 128.9 (2 × CH), 129.2 (2 × CH), 130.9 (C), 131.1 (C), 151.7 (C), 152.6 (C), 159.8 (C), 161.2 (C); *m/z* (ESI) 557.0510 (MNa^+. $C_{24}H_{21}{}^{35}Cl_3N_4NaO_4$ requires 557.0521).

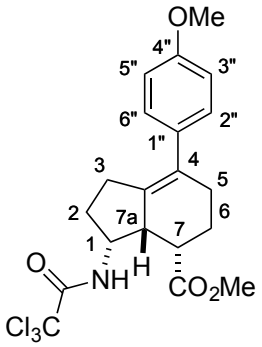
Method B- (9*R**,9a*S**)-6-(4”-Methoxyphenyl)-2-phenyl-7,8,9,9a-tetrahydro-9-(2’,2’,2’-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (**211**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-(4”-methoxyphenyl)-2-phenyl-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**210**) (Method B) using 7-(4”-methoxyphenyl)-3-(2’,2’,2’-trichloromethylcarbonylamino)hept-1-en-6-yne (**188**) (0.033 g, 0.090 mmol) and 4-phenyl-1,2,4-triazole-3,5-dione (0.020 g, 0.11 mmol). The Diels-Alder reaction was stirred for 24 h at 75 °C. Purification by flash column chromatography (petroleum ether/ethyl acetate, 6:4) gave (9*R**,9a*S**)-6-(4”-methoxyphenyl)-2-phenyl-7,8,9,9a-tetrahydro-9-(2’,2’,2’-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (**211**) (0.037 g, 76%) as a dark yellow solid. Spectroscopic data was as described above.

(1*R,7a*R**)-2,3,5,6,7,7a-Hexahydro-4-(4”-methoxyphenyl-6,6,7,7-tetracyano-1-(2’,2’,2’-trichloromethylcarbonylamino)indene (212)**



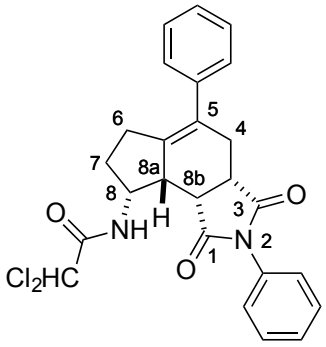
(1*R**,7a*R**)-2,3,5,6,7,7a-Hexahydro-4-(4”-methoxyphenyl-6,6,7,7-tetracyano-1-(2’,2’,2’-trichloromethylcarbonylamino)indene (**212**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-(4”-methoxyphenyl)-2-phenyl-8-(2’,2’,2’-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**210**) (Method B) using 7-(4”-methoxyphenyl)-3-(2’,2’,2’-trichloromethylcarbonylamino)hept-1-en-6-yne (**188**) (0.036 g, 0.10 mmol) and tetracyanoethylene (0.080 g, 0.60 mmol). The Diels-Alder reaction was stirred for 24 h at 75 °C. Purification by flash column chromatography (petroleum ether/ethyl acetate, 6:4) gave (1*R**,7a*R**)-2,3,5,6,7,7a-hexahydro-4-(4”-methoxyphenyl-6,6,7,7-tetracyano-1-(2’,2’,2’-trichloromethylcarbonylamino)indene (**212**) (0.03 g, 57%) as a yellow solid. Mp 116–118 °C; ν_{max}/cm^{-1} (neat) 3370 (NH), 2935 (CH), 1711 (C=O), 1513 (C=C), 1248, 1178, 824; δ_H (400 MHz, $CDCl_3$) 1.88–2.02 (1H, m, 2-*H*H), 2.33–2.47 (2H, m, 2-H*H* and 3-*H*H), 2.64–2.77 (1H, m, 3-H*H*), 3.24–3.33 (1H, m, 5-*H*H), 3.44–3.54 (2H, m, 5-H*H* and 7a-H), 3.84 (3H, s, OCH_3), 4.39–4.51 (1H, m, 1-H), 6.91–6.97 (3H, m, 3”-H, 5”-H and NH), 7.11–7.15 (2H, m, 2”-H and 6”-H); δ_C (101 MHz, $CDCl_3$) 26.4 (CH_2), 29.1 (CH_2), 37.6 (CH_2), 39.7 (C), 41.4 (C), 50.0 (CH), 54.9 (CH), 55.4 (CH_3), 91.7 (C), 108.2 (C), 110.4 (C), 110.7 (C), 110.8 (C), 114.5 (2 × CH), 127.5 (C), 128.4 (2 × CH), 128.6 (C), 130.5 (C), 159.9 (C), 162.5 (C); *m/z* (ESI) 510.0253 (MNa^+. $C_{22}H_{16}{}^{35}Cl_3N_5NaO_2$ requires 510.0262).

Methyl (1*R,7*S**,7a*S**)-2,3,5,6,7,7a-hexahydro-4-(4''-methoxyphenyl)-1-(2',2',2'-trichloromethylcarbonylamino)indene-7-carboxylate (213)**



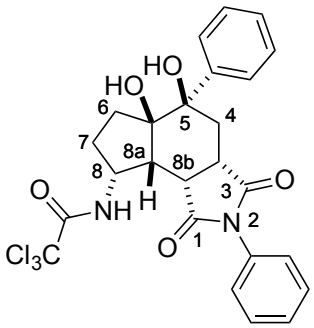
Methyl (1*R**,7*S**,7a*S**)-2,3,5,6,7,7*a*-hexahydro-4-(4''-methoxyphenyl)-1-(2',2',2'-trichloromethylcarbonylamino)indene-7-carboxylate (**213**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-(4''-methoxyphenyl)-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**210**) (Method B) using 7-(4''-methoxyphenyl)-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**188**) (0.040 g, 0.11 mmol) and methyl acrylate (0.030 mL, 0.33 mmol). The Diels-Alder reaction was stirred for 5 days at 111 °C. Purification by flash column chromatography (petroleum ether/diethyl ether, 7:3) gave methyl (1*R**,7*S**,7a*S**)-2,3,5,6,7,7a-hexahydro-4-(4''-methoxyphenyl)-1-(2',2',2'-trichloromethylcarbonylamino)indene-7-carboxylate (**213**) (0.028 g, 59%) as a pale yellow oil; ν_{max}/cm^{-1} (neat) 3350 (NH), 2935 (CH), 1712 (C=O), 1608, 1510 (C=C), 1246, 1175, 1035, 822, 737; δ_H (400 MHz, $CDCl_3$) 1.64–1.76 (1H, m, 2-*H*H), 1.93–2.08 (2H, m, 2-H*H*, and 6-*H*H), 2.21–2.38 (3H, m, 3-*H*H, 5-*H*H and 6-H*H*), 2.40–2.59 (2H, m, 3-H*H* and 5-H*H*), 2.99 (1H, q, *J* 4.6 Hz, 7-H), 3.03–3.11 (1H, m, 7a-H), 3.71 (1H, s, OCH_3), 3.81 (1H, s, OCH_3), 4.63 (1H, qd, *J* 9.0, 6.9 Hz, 1-H), 6.84–6.89 (2H, m, 3''-H and 5''-H), 7.10–7.16 (2H, m, 2''-H and 6''-H), 7.68 (1H, d, *J* 9.0 Hz, NH); δ_C (101 MHz, $CDCl_3$) 26.4 (CH_2), 27.8 (CH_2), 29.0 (CH_2), 31.6 (CH_2), 39.5 (CH), 43.9 (CH), 52.1 (CH), 53.2 (CH_3), 55.3 (CH_3), 92.9 (C), 113.4 (2 × CH), 128.7 (2 × CH), 129.4 (C), 134.3 (C), 135.1 (C), 158.3 (C), 161.7 (C), 175.5 (C); *m/z* (ESI) 468.0486 (MNa^+. $C_{20}H_{22}{}^{35}Cl_3NNaO_4$ requires 468.0507).

(3a*S,8*R**,8a*S**,8b*R**)-2,5-Diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2′,2′-dichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (214)**



To a solution of (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2′,2′,2′-trichloromethylcarbonylamino)cyclopent[*e*]iso-indole-1,3(2*H*,3a*H*)-dione (**201**) (0.080 g, 0.16 mmol) in ethyl acetate (4 mL) was added 10% palladium on charcoal (0.020 g). The mixture was stirred under an atmosphere of hydrogen at room temperature for 48 h. The reaction mixture was filtered through a short pad of Celite® with diethyl ether (80 mL) and the solvent was removed *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2′,2′-dichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**214**) (0.036 g, 48%) as a white solid. Mp 138–140 °C; ν_{max}/cm^{-1} (neat) 3323 (NH), 2922 (CH), 1690 (CO), 1524 (C=C), 1497, 1389, 1196, 808, 734; δ_H (400 MHz, $CDCl_3$) 1.66–1.80 (1H, m, 7-*H*H), 2.05–2.15 (1H, m, 7-H*H*), 2.52–2.64 (3H, m, 4-*H*H and 6-H_2), 3.07 (1H, dd, *J* 8.7, 6.4 Hz, 8a-H), 3.29 (1H, dd, *J* 15.3, 2.9 Hz, 4-H*H*), 3.44–3.54 (2H, m, 3a-H and 8b-H), 4.89–5.01 (1H, m, 8-H), 5.99 (1H, s, $CHCl_2$), 7.06–7.12 (2H, m, 2 × ArH), 7.22–7.53 (8H, m, 8 × ArH), 8.66 (1H, d, *J* 9.7 Hz, NH); δ_C (126 MHz, $CDCl_3$) 28.4 (CH_2), 31.7 (2 × CH_2), 40.3 (CH), 41.7 (CH), 43.7 (CH), 51.6 (CH), 66.7 (CH), 126.6 (2 × CH), 127.2 (CH), 127.5 (2 × CH), 128.4 (2 × CH), 129.1 (CH), 129.4 (2 × CH), 130.1 (C), 131.5 (C), 139.0 (C), 139.9 (C), 164.6 (C), 178.6 (C), 179.7 (C); *m/z* (EI) 468.1012 (M^+. $C_{25}H_{22}{}^{35}Cl_2N_2O_3$ requires 468.1007), 341 (100%), 194 (71), 167 (34), 152 (11), 77 (11).

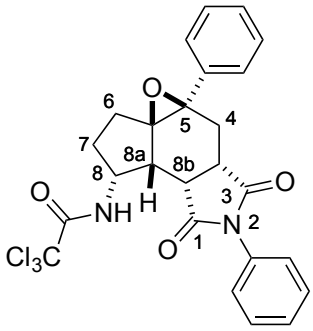
(3a*S*,5R*,5*a*R,8*R**,8a*R**,8b*R**)-5,5a-Dihydroxy-2,5-diphenyl-3a,4,5,5a,6,7,8a,8b-octahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (216)**



(3a*S**,8*R**,8a*S**,8b*R**)-2,5-Diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (0.040 g, 0.080 mmol) was dissolved in dichloromethane (2 mL) at –78 ºC. Tetramethylethylenediamine (0.013 mL, 0.090 mmol) was added and the reaction mixture stirred for 0.1 h, before the addition of osmium tetroxide (0.020 g, 0.090 mmol). The dark coloured solution was stirred for 1 h at –78 ºC before warming to room temperature and then stirred for 2 h. The solvent was removed *in vacuo* and the dark coloured solid was dissolved in methanol (2 mL). 12 M Hydrochloric acid (0.5 mL) was added and the reaction stirred for a further 2 h. The solvent was removed *in vacuo* to afford a dark solid. Flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave (3a*S*,5R*,5*a*R**,8*R**,8a*R**,8b*R**)-5,5a-dihydroxy-2,5-diphenyl-3a,4,5,5a,6,7,8a,8b-octahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**216**) (0.040 g, 100%) as a white solid. Mp 164–166 °C; ν_{max}/cm^{-1} (neat) 3475 (NH/OH), 2931 (CH), 1698 (C=O), 1500 (C=C), 1380, 1216, 818, 753; δ_H (500 MHz, CD_3OD) 1.13–1.23 (1H, m, 6-*H*H), 1.86–2.06 (2H, m, 6-H*H* and 7-*H*H), 2.14–2.30 (2H, m, 4-*H*H and 7-H*H*), 2.58 (1H, dd, *J* 14.3, 12.5 Hz, 4-H*H*), 2.87–2.93 (1H, m, 8a-H), 3.41–3.49 (2H, m, 3a-H), 3.59 (1H, t, *J* 7.6 Hz, 8b-H), 5.10 (1H, dt, *J* 10.8, 7.6 Hz, 8-H), 7.21–7.27 (1H, m, ArH), 7.29–7.38 (4H, m, 4 × ArH), 7.40–7.46 (1H, m, ArH), 7.47–7.58 (4H, m, 4 × ArH); δ_C (126 MHz, CD_3OD) 27.8 (CH_2), 30.6 (CH_2), 36.2 (CH_2), 39.9 (CH), 41.6 (CH), 46.0 (CH), 52.0 (CH), 74.5 (C), 83.7 (C), 92.7 (C), 126.4 (2 × CH), 126.7 (CH), 126.8 (2 × CH), 127.3 (2 × CH), 128.4 (CH), 128.7 (2 × CH), 132.0 (C), 143.5 (C), 162.0 (C), 178.7 (C), 178.8 (C); *m/z* (ESI)

559.0564 (MNa^+. $C_{25}H_{23}{}^{35}Cl_3N_2NaO_5$ requires 559.0565).

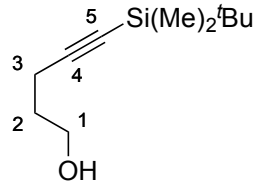
(3a*S*,5R*,5*a*R*,8*R,8a*R**,8b*R**)-5,5a-Epoxy-2,5-diphenyl-3a,4,5,5a,6,7,8a,8b-octahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (217)**



3-Chloroperbenzoic acid (0.030 g, 0.18 mmol) was added to a stirred solution of (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (0.020 g, 0.044 mmol) in dichloromethane (2 mL) at 0 °C. The reaction mixture was warmed from 0 °C to room temperature over 18 h then cooled to 0 °C before 3-chloroperbenzoic acid (0.030 g, 0.18 mmol) was added. The reaction mixture was stirred for a further 24 h at room temperature, quenched by the addition of a saturated solution of sodium sulfite (3 mL) and extracted with dichloromethane (2 × 3 mL). The combined organic layers were washed with a saturated solution of sodium hydrogen carbonate (3 × 6 mL), water (6 mL), brine (6 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 1:1) gave (3a*S*,5R*,5*a*R*,8*R**,8a*R**,8b*R**)-5,5a-epoxy-2,5-diphenyl-3a,4,5,5a,6,7,8a,8b-octahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**217**) (0.015 g, 65%) as a white solid. Mp 142–144 °C; ν_{max}/cm^{-1} (neat) 3340 (NH), 2921 (CH), 1701 (C=O), 1514 (C=C), 1390, 1192, 821, 756; δ_H (400 MHz, $CDCl_3$) 1.58−1.71 (1H, m, 6-*H*H), 1.85−1.99 (2H, m, 6-H*H* and 7-*H*H), 2.23−2.33 (2H, m, 4-*H*H and 7-H*H*), 2.75 (1H, dd, *J* 9.0, 7.1 Hz, 8a-H), 3.22 (1H, dd, *J* 15.9 Hz, 1.3, 4-H*H*), 3.40 (1H, dd, *J* 9.3, 7.1 Hz, 8b-H), 3.49 (1H, td, *J* 9.3, 1.3 Hz, 3a-H), 5.02−5.13 (1H, m, 8-H), 7.11−7.15 (2H, m, 2 × ArH), 7.21−7.37 (5H, m, 5 × ArH), 7.42−7.55 (3H, m, 3 × ArH), 8.52 (1H, d, *J* 9.3 Hz,

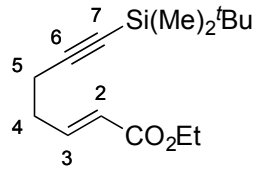
NH); δ_C (101 MHz, $CDCl_3$) 25.1 (CH_2), 29.5 (CH_2), 33.0 (CH_2), 38.3 (CH), 40.0 (CH), 45.5 (CH), 52.0 (CH), 61.6 (C), 71.8 (C), 92.7 (C), 126.0 (2 × CH), 126.5 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 129.4 (CH), 129.5 (2 × CH), 131.2 (C), 136.9 (C), 162.0 (C), 178.5 (C), 178.9 (C); *m/z* (ESI) 541.0450 (MNa^+. $C_{25}H_{21}{}^{35}Cl_3N_2NaO_4$ requires 541.0459).

5-(*tert*-Butyldimethylsilyl)pent-4-yn-1-ol (222)[203]



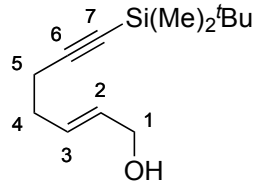
n-Butyllithium (0.520 mL, 1.31 mmol, 2.5 M in hexane) was added dropwise to a solution of 4-pentyn-1-ol (**168**) (0.0500 g, 0.590 mmol) in tetrahydrofuran (20 mL) at −78 °C. The reaction mixture was stirred for 0.75 h at −78 °C. *tert*-Butyldimethylsilyl chloride (0.220 g, 1.48 mmol) was then added. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. A 1 M aqueous solution of hydrochloric acid (2 mL) was then added and the mixture was stirred for 2 h. The resulting mixture was diluted with ethyl acetate (10 mL), washed with water (2 × 15 mL) and a saturated solution of sodium bicarbonate (15 mL). The aqueous layers were washed with ethyl acetate (2 × 15 mL), and the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 5-(*tert*-butyldimethylsilyl)pent-4-yn-1-ol (**222**) (0.036 g, 31%) as a colourless oil. Spectroscopic data was consistent with the literature.[203] δ_H (400 MHz, $CDCl_3$) 0.06 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.75 (2H, quin, *J* 6.5 Hz, 2-H_2), 1.99 (1H, br s, OH), 2.34 (2H, t, *J* 6.5 Hz, 3-H_2), 3.74 (2H, t, *J* 6.5 Hz, 1-H_2); δ_C (101 MHz, $CDCl_3$) −4.5 (2 × CH_3), 16.5 (C), 16.5 (CH_2), 26.1 (3 × CH_3), 31.3 (CH_2), 61.8 (CH_2), 83.3 (C), 107.2 (C); *m/z* (ESI) 221 (MNa^+. 100%).

Ethyl (2*E*)-7-(*tert*-butyldimethylsilyl)hept-2-en-6-ynoate (223)



Ethyl (2*E*)-7-(*tert*-butyldimethylsilyl)hept-2-en-6-ynoate (**223**) was synthesised as described for ethyl (2*E*)-hept-2-en-6-ynoate (**174**) using 5-(*tert*-butyldimethylsilyl)-pent-4-yn-1-ol (**222**) (0.196 g, 0.990 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave ethyl (2*E*)-7-(*tert*-butyldimethylsilyl)hept-2-en-6-ynoate (**223**) (0.211 g, 80%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2929 (CH), 2364, 1723 (C=O), 1472, 1250, 1040, 837; δ_H (400 MHz, $CDCl_3$) 0.07 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.34–2.45 (4H, m, 4-H_2 and 5-H_2), 4.18 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.88 (1H, d, *J* 15.7 Hz, 2-H), 6.97 (1H, dt, *J* 15.7, 6.6 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) −4.6 (2 × CH_3), 14.2 (CH_3), 16.4 (C), 18.8 (CH_2), 26.0 (3 × CH_3), 31.3 (CH_2), 60.2 (CH_2), 84.0 (C), 105.8 (C), 122.5 (CH), 146.5 (CH), 166.3 (C); *m/z* (ESI) 289.1590 (MNa^+. $C_{15}H_{26}NaO_2Si$ requires 289.1594).

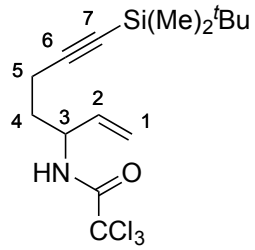
(2*E*)-7-(*tert*-Butyldimethylsilyl)hept-2-en-6-yn-1-ol (224)



(2*E*)-7-(*tert*-butyldimethylsilyl)hept-2-en-6-yn-1-ol (**224**) was synthesised as described for (2*E*)-hept-2-en-6-yn-1-ol (**179**) using ethyl (2*E*)-7-(*tert*-butyldimethylsilyl)hept-2-en-6-ynoate (**223**) (0.165 g, 0.620 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave (2*E*)-7-(*tert*-butyldimethylsilyl)hept-2-en-6-yn-1-ol (**224**) (0.128 g, 92%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3332 (OH), 2929 (CH), 2174, 1472, 1250, 1007, 968, 837, 825, 774; δ_H (400 MHz, $CDCl_3$) 0.07 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.32 (1H, br s, OH), 2.23–2.39 (4H, m, 4-H_2 and 5-H_2), 4.09 (2H, br t, *J* 4.6 Hz, 1-H_2), 5.66–5.78 (2H, m, 2-H and 3-H); δ_C (101 MHz, $CDCl_3$) −4.5 (2 × CH_3), 16.5 (C),

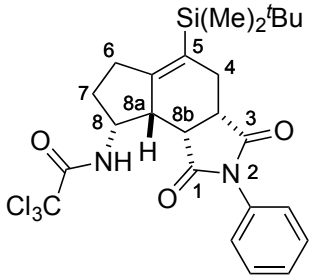
19.9 (CH_2), 26.0 (3 × CH_3), 31.5 (CH_2), 63.5 (CH_2), 83.1 (C), 107.0 (C), 130.4 (CH), 130.8 (CH); *m/z* (ESI) 247.1479 (MNa^+. $C_{13}H_{24}NaOSi$ requires 247.1489).

7-(*tert*-Butyldimethylsilyl)-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (226)



7-(*tert*-Butyldimethylsilyl)-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**226**) was synthesised as described for 3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**184**), except using (2*E*)-7-(*tert*-butyldimethylsilyl)hept-2-en-6-yn-1-ol (**224**) (0.052 g,0.23 mmol) and a single portion of bis(acetonitrile)palladium chloride (0.0060 g, 0.023 mmol). The reaction was performed at 20 °C for 12 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave 7-(*tert*-butyldimethylsilyl)-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**226**) (0.068 g, 80%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3331 (NH), 2928 (CH), 1695 (C=O), 1516 (C=C), 1250, 837, 824, 775, 681; δ_H (400 MHz, $CDCl_3$) 0.08 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.82–1.98 (2H, m, 4-H_2), 2.27–2.41 (2H, m, 5-H_2), 4.48–4.57 (1H, m, 3-H), 5.22–5.32 (2H, m, 1-H_2), 5.81 (1H, ddd, *J* 17.0, 10.4, 5.8 Hz, 2-H), 6.68 (1H, d, *J* 7.0 Hz, NH); δ_C (101 MHz, $CDCl_3$) −4.5 (2 × CH_3), 16.5 (CH_2), 16.5 (C), 26.1 (3 × CH_3), 33.2 (CH_2), 53.2 (CH), 84.2 (C), 92.7 (C), 105.9 (C), 116.9 (CH_2), 135.6 (CH), 161.2 (C); *m/z* (ESI) 390.0568 (MNa^+. $C_{15}H_{24}{}^{35}Cl_3NNaOSi$ requires 390.0585).

(3a*S*,8*R***,8a*S***,8b*R***)-5-(*tert*-Butyldimethylsilyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (227)**

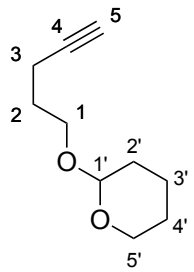


Method A- (3a*S***,8*R***,8a*S***,8b*R***)-5-(*tert*-Butyldimethylsilyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**227**) was synthesised as described for (3a*S***,8*R***,8a*S***,8b*R***)-3a,4,6,7,8a,8b-hexahydro-5-(4"-methoxyphenyl)-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**210**) (Method B) using 7-(*tert*-butyldimethylsilyl)-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**226**) (0.044 g, 0.12 mmol), except that the reaction mixture was stirred with Grubbs second generation catalyst (0.010 g, 0.012 mmol) and 1,7-octadiene (0.071 mL, 0.48 mmol) for 60 h at 90 °C. A second portion of Grubbs second generation catalyst (0.010 g, 0.012 mmol) was added with 1,7-octadiene (0.071 mL, 0.48 mmol) and the reaction mixture was stirred for further 60 h at 90 °C. *N*-Phenyl maleimide (0.031 g, 0.18 mmol) was added with hydroquinone (0.002 g, 0.020 mmol). The reaction mixture was stirred for 18 h at 75 °C. The reaction mixture was then cooled and the solvent was evaporated. Flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave (3a*S***,8*R***,8a*S***,8b*R***)-5-(*tert*-butyldimethylsilyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**227**) (0.013 g, 20%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3319 (NH), 2954 (CH), 1699 (C=O), 1517 (C=C), 1388, 1199, 827, 755; δ_H (400 MHz, $CDCl_3$) 0.08 (3H, s, $SiCH_3$), 0.15 (3H, s, $SiCH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 1.83 (1H, ddd, *J* 18.6, 12.4, 7.6 Hz, 7-*H*H), 2.12–2.21 (2H, m, 4-*H*H and 7-H*H*), 2.24–2.38 (1H, m, 6-*H*H), 2.65 (1H, dd, *J* 16.5, 7.6 Hz, 6-H*H*), 2.92–2.98 (1H, m, 8a-H), 3.01 (1H, dd, *J* 14.8, 1.3 Hz, 4-H*H*), 3.32 (1H, ddd, *J* 8.9, 7.2, 1.3 Hz, 3a-H), 3.40 (1H, dd, *J* 8.9, 6.3 Hz, 8b-H), 4.77–4.88 (1H, m, 8-H), 7.12–7.17 (2H, m, 2 × ArH), 7.37–7.50 (3H, m, 3 ×

ArH), 8.84 (1H, d, *J* 9.6 Hz, NH); δ_C (126 MHz, $CDCl_3$) −5.1 (CH_3), −4.2 (CH_3), 18.3 (C), 26.8 (3 × CH_3), 30.3 (CH_2), 30.5 (CH_2), 31.9 (CH_2), 39.3 (CH), 40.6 (CH), 43.1 (CH), 52.3 (CH), 92.9 (C), 126.4 (2 × CH), 128.8 (C), 129.0 (CH), 129.3 (2 × CH), 131.5 (C), 156.1 (C), 162.3 (C), 178.1 (C), 179.8 (C); *m/z* (ESI) 563.1045 (MNa^+. $C_{25}H_{31}{}^{35}Cl_3N_2NaO_3Si$ requires 563.1062).

Method B- (3a*S**,8*R**,8a*S**,8b*R**)-5-(*tert*-Butyldimethylsilyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**227**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method A) using (2*E*)-7-(*tert*-Butyldimethylsilyl)hept-2-en-6-yn-1-ol (**224**) (0.054 g, 0.24 mmol), except that the reaction mixture was stirred with Grubbs second generation catalyst (0.040 g, 0.048 mmol) and 1,7-octadiene (0.142 mL, 0.960 mmol) for 120 h at 110 °C. *N*-Phenyl maleimide (0.062 g, 0.36 mmol) was added with hydroquinone (0.003 g, 0.030 mmol). The reaction mixture was stirred for 18 h at 75 °C. The reaction mixture was then cooled and the solvent was evaporated. Flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave (3a*S**,8*R**,8a*S**,8b*R**)-5-(*tert*-butyldimethylsilyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**227**) (0.025 g, 19%) as a yellow oil. Spectroscopic data was as described above.

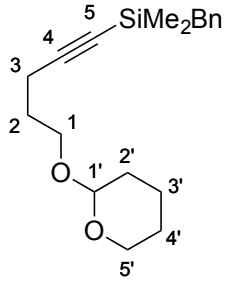
1-(Tetrahydropyran-2'-yloxy)-4-pentyne (228)[204]



To a solution of 4-pentyn-1-ol (**168**) (0.900 g, 10.8 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (0.020 g) in dichloromethane (25 mL) at 0 °C was added 3,4-dihydro-2*H*-pyran (2.71 g, 32.2 mmol). The reaction mixture was

allowed to warm to room temperature and stirred for 2.5 h. Ethyl acetate (50 mL) was then added and the solution was poured into a solution of sodium hydrogen carbonate (100 mL). The mixture was then extracted with ethyl acetate (3 × 50 mL). The organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 10:1) gave 1-(tetrahydropyran-2'-yloxy)-4-pentyne (**228**) (1.81 g, 100%) as a colourless oil. Spectroscopic data was consistent with the literature.[204] δ_H (400 MHz, $CDCl_3$) 1.46−1.86 (8H, m, 2-H_2, 3'-H_2, 4'-H_2 and 5'-H_2), 1.94 (1H, t, *J* 2.7 Hz, 5-H), 2.28−2.35 (2H, m, 3-H_2), 3.45−3.55 (2H, m, 1-*H*H and 6'-*H*H), 3.80−3.91 (2H, m, 1-H*H* and 6'-H*H*), 4.60 (1H, t, *J* 3.3 Hz, 2'-H); δ_C (101 MHz, $CDCl_3$) 15.1 (CH_2), 19.2 (CH_2), 25.4 (CH_2), 28.6 (CH_2), 30.4 (CH_2), 61.7 (CH_2), 65.4 (CH_2), 68.5 (CH), 83.6 (C), 98.4 (CH); *m/z* (EI) 168 (M^+. 4%), 149 (8), 125 (11), 111 (12), 84 (74), 67 (28), 49 (100).

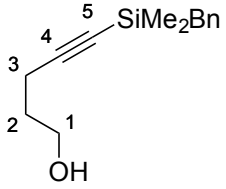
5-(Benzyldimethylsilyl)-1-(tetrahydropyran-2'-yloxy)pent-4-yne (229)[205]



n-Butyllithium (2.56 mL, 6.40 mmol, 2.5 M in hexane) was slowly added to a stirred solution of 1-(tetrahydropyran-2'-yloxy)-4-pentyne (**228**) (0.980 g, 5.82 mmol) in tetrahydrofuran (28 mL) at −78 °C. The resulting solution was stirred at –78 °C for 0.5 h at which time benzyldimethylsilyl chloride (1.16 mL, 6.40 mmol) was added. The resulting solution was stirred at –78 °C for 5 h. The reaction was quenched with a saturated solution of ammonium chloride (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 8:2) gave 5-(benzyldimethylsilyl)-1-(tetrahydropyran-2'-yloxy)-4-pentyne (**229**) (1.84 g, 100%) as a colourless oil. Spectroscopic data was consistent with the literature.[205] δ_H (400 MHz, $CDCl_3$) 0.10 (6H, s, $Si(CH_3)_2$), 1.47−1.87 (8H, m, 2-H_2, 3'-H_2, 4'-H_2 and 5'-H_2), 2.18 (2H, s,

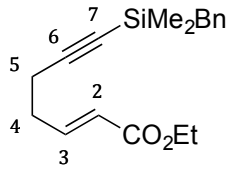
$SiCH_2$), 2.35 (2H, t, *J* 7.1 Hz, 3-H_2), 3.42−3.54 (2H, m, 1-*H*H and 6'-*H*H), 3.79−3.91 (2H, m, 1-H*H* and 6'-H*H*), 4.60 (1H, t, *J* 3.3 Hz, 2'-H), 7.05−7.12 (3H, m, 3 × ArH), 7.19−7.25 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 0.0 (2 × CH_3), 18.7 (CH_2), 21.4 (CH_2), 27.4 (CH_2), 28.4 (CH_2), 30.7 (CH_2), 32.6 (CH_2), 64.0 (CH_2), 67.7 (CH_2), 85.0 (C), 100.6 (CH), 110.2 (C), 126.2 (CH), 130.0 (2 × CH), 130.3 (2 × CH), 141.1 (C); *m/z* (ESI) 339 (MNa^+. 100%).

5-(Benzyldimethylsilyl)pent-4-yn-1-ol (230)[125]



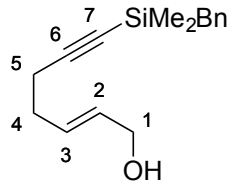
p-Toluenesulfonic acid monohydrate (8.00 mg, 0.042 mmol) was added to a solution of 5-(benzyldimethylsilyl)-1-(tetrahydropyran-2'-yloxy)pent-4-yne (**229**) (85.0 mg, 0.270 mmol) in methanol (3 mL). The resulting solution was stirred at room temperature for 18 h. The reaction was quenched by addition of brine (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 1:1) gave 5-(benzyldimethylsilyl)pent-4-yn-1-ol (**230**) (0.065 g, 100%) as a colourless oil. Spectroscopic data was consistent with the literature.[125] δ_H (400 MHz, $CDCl_3$) 0.12 (6H, s, $Si(CH_3)_2$), 1.76 (2H, quin, *J* 6.5 Hz, 2-H_2), 1.86 (1H, s, OH), 2.19 (2H, s, $SiCH_2$), 2.35 (2H, t, *J* 6.5 Hz, 3-H_2), 3.72 (2H, t, *J* 6.5 Hz, 1-H_2), 7.06–7.13 (3H, m, 3 × ArH), 7.21–7.27 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 0.0 (2 × CH_3), 18.4 (CH_2), 28.4 (CH_2), 33.0 (CH_2), 63.6 (CH_2), 85.5 (C), 110.0 (C), 126.2 (CH), 130.0 (2 × CH), 130.3 (2 × CH), 141.1 (C); *m/z* (ESI) 255 (MNa^+. 100%).

Ethyl (2*E*)-7-(benzyldimethylsilyl)hept-2-en-6-ynoate (231)



Ethyl (2*E*)-7-(benzyldimethylsilyl)hept-2-en-6-ynoate (**231**) was synthesised as described for ethyl (2*E*)-hept-2-en-6-ynoate (**174**) using 5-(benzyldimethylsilyl)pent-4-yn-1-ol (**230**) (0.990 g, 4.28 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 8:2) gave ethyl (2*E*)-7-(benzyldimethylsilyl)hept-2-en-6-ynoate (**231**) (1.19 g, 92%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2958 (CH), 1720 (C=O), 1656 (C=C), 1494, 1249, 1154, 1039, 833, 758; δ_H (400 MHz, $CDCl_3$) 0.10 (6H, s, $Si(CH_3)_2$), 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.18 (2H, s, $SiCH_2$), 2.34–2.45 (4H, m, 4-H_2 and 5-H_2), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.87 (1H, dt, *J* 15.7, 1.4 Hz, 2-H), 6.97 (1H, dt, *J* 15.7, 6.6 Hz, 3-H), 7.03–7.12 (3H, m, 3 × ArH), 7.19–7.25 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 0.0 (2 × CH_3), 16.3 (CH_3), 20.8 (CH_2), 28.3 (CH_2), 33.1 (CH_2), 62.2 (CH_2), 86.3 (C), 108.8 (C), 124.5 (CH), 126.3 (CH), 130.1 (2 × CH), 130.3 (2 × CH), 141.0 (C), 148.4 (CH), 168.2 (C); *m/z* (ESI) 323.1422 (MNa^+. $C_{18}H_{24}NaO_2Si$ requires 323.1438).

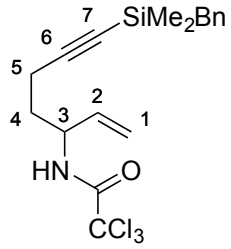
(2*E*)-7-(Benzyldimethylsilyl)hept-2-en-6-yn-1-ol (232)



(2*E*)-7-(Benzyldimethylsilyl)hept-2-en-6-yn-1-ol (**232**) was synthesised as described for (2*E*)-hept-2-en-6-yn-1-ol (**179**) using ethyl (2*E*)-7-(benzyldimethylsilyl)hept-2-en-6-ynoate (**231**) (1.35 g, 4.49 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave (2*E*)-7-(benzyldimethylsilyl)hept-2-en-6-yn-1-ol (**232**) (1.14 g, 98%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3367 (OH), 2922 (CH), 2175, 1494, 1249, 838, 762, 698; δ_H (500 MHz, $CDCl_3$) 0.11 (6H, s, $Si(CH_3)_2$), 1.43 (1H, br s, OH), 2.18 (2H, s, $SiCH_2$),

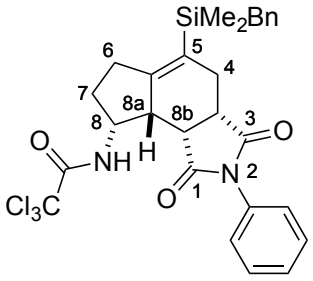
2.23–2.34 (4H, m, 4-H_2 and 5-H_2), 4.10 (2H, d, *J* 4.4 Hz, 1-H_2), 5.65–5.76 (2H, m, 2-H and 3-H), 7.06–7.12 (3H, m, 3 × ArH), 7.20–7.25 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 0.0 (2 × CH_3) 21.8 (CH_2), 28.4 (CH_2), 33.2 (CH_2), 65.4 (CH_2), 85.5 (C), 109.9 (C), 126.2 (CH), 130.0 (2 × CH), 130.3 (2 × CH), 132.3 (CH), 132.6 (CH), 141.1 (C); *m/z* (ESI) 281.1323 (MNa^+. $C_{16}H_{22}NaOSi$ requires 281.1332).

7-(Benzyldimethylsilyl)-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (233)



7-(Benzyldimethylsilyl)-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**233**) was synthesised as described for 3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**184**), except using (2*E*)-7-(benzyldimethylsilyl)hept-2-en-6-yn-1-ol (**232**) (0.11 g, 0.43 mmol) and a single portion of bis(acetonitrile)palladium chloride (0.011 g, 0.043 mmol). The reaction was performed at 20 °C for 12 h. Purification by flash column chromatography (petroleum ether/diethyl ether, 8:2) gave 7-(benzyldimethylsilyl)-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**233**) (0.116 g, 68%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3345 (NH), 2961 (CH), 1696 (C=O), 1514 (C=C), 1494, 1250, 832, 822, 797, 763, 699; δ_H (400 MHz, $CDCl_3$) 0.12 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 1.81–1.97 (2H, m, 4-H_2), 2.19 (2H, s, $SiCH_2$), 2.27–2.41 (2H, m, 5-H_2), 4.47–4.56 (1H, m, 3-H), 5.23–5.31 (2H, m, 1-H_2), 5.81 (1H, ddd, *J* 17.2, 10.4, 5.8 Hz, 2-H), 6.72 (1H, d, *J* 7.7 Hz, NH), 7.04–7.12 (3H, m, 3 × ArH), 7.19–7.25 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 0.0 (CH_3), 0.0 (CH_3), 18.4 (CH_2), 28.3 (CH_2), 34.7 (CH_2), 55.1 (CH), 86.5 (C), 94.7 (C), 108.8 (C), 118.8 (CH_2), 126.3 (CH), 130.1 (2 × CH), 130.3 (2 × CH), 137.5 (CH), 141.0 (C), 163.2 (C); *m/z* (ESI) 424.0413 (MNa^+. $C_{18}H_{22}{}^{35}Cl_3NNaOSi$ requires 424.0428).

(3a*S*,8*R***,8a*S***,8b*R***)-5-(Benzyldimethylsilyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (235)**

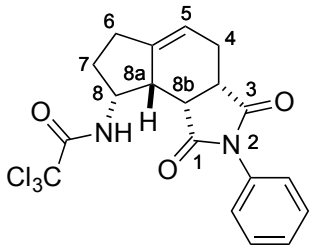


Method A- (3a*S**,8*R**,8a*S**,8b*R**)-5-(Benzyldimethylsilyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**235**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-(4"-methoxyphenyl)-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**210**) (Method B) using 7-(benzyldimethylsilyl)-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**233**) (0.056 g, 0.14 mmol), except that the reaction mixture was stirred with Grubbs second generation catalyst (0.0080 g, 0.010 mmol) and 1,7-octadiene (0.083 mL, 0.56 mmol) for 18 h at 90 °C. Flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave (3a*S**,8*R**,8a*S**,8b*R**)-5-(benzyldimethylsilyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**235**) (0.053 g, 66%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3313 (NH), 3023 (CH), 2957 (CH), 1698 (C=O), 1518 (C=C), 1389, 1198, 830, 754; δ_H (500 MHz, $CDCl_3$) 0.05 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 1.73–1.89 (1H, m, 7-*H*H), 2.06–2.27 (5H, m, $SiCH_2$, 4-*H*H, 6-*H*H and 7-H*H*), 2.52 (1H, dd, *J* 16.5, 7.6 Hz, 6-H*H*), 2.90–2.96 (1H, m, 8a-H), 2.99 (1H, dd, *J* 14.7, 1.6 Hz, 4-H*H*), 3.34 (1H, ddd, *J* 8.9, 6.8, 1.6 Hz, 3a-H), 3.42 (1H, dd, *J* 8.9, 6.5 Hz, 8b-H), 4.75–4.88 (1H, m, 8-H), 6.91–6.96 (2H, m, 2 × ArH), 7.04–7.10 (1H, m, ArH), 7.14–7.21 (4H, m, 4 × ArH), 7.38–7.50 (3H, m, 3 × ArH), 8.91 (1H, d, *J* 9.5 Hz, NH); δ_C (126 MHz, $CDCl_3$) −3.2 (CH_3), −2.6 (CH_3), 25.2 (CH_2), 29.4 (CH_2), 29.8 (CH_2), 31.9 (CH_2), 39.5 (CH), 40.7 (CH), 43.1 (CH), 52.3 (CH), 92.9 (C), 124.3 (CH), 126.3 (2 × CH), 128.2 (2 × CH), 128.3 (2 × CH), 129.0 (C), 129.1 (CH), 129.4 (2 × CH), 131.5 (C), 139.3 (C), 155.7 (C), 162.3

(C), 178.4 (C), 179.9 (C); *m/z* (ESI) 597.0898 (MNa^+. $C_{28}H_{29}{}^{35}Cl_3N_2NaO_3Si$ requires 597.0905).

Method B- (3a*S**,8*R**,8a*S**,8b*R**)-5-(Benzyldimethylsilyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**235**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method A) using (2*E*)-7-(benzyldimethylsilyl)hept-2-en-6-yn-1-ol (**232**) (0.500 g, 1.92 mmol), except that the reaction mixture was stirred with *N*-phenyl maleimide (0.500 g, 2.87 mmol) and hydroquinone (0.026 g, 0.24 mmol) at 75 °C for 12 h. Purification by flash column chromatography (petroleum ether/diethyl ether, 9:1) gave (3a*S**,8*R**,8a*S**,8b*R**)-5-(benzyldimethylsilyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**235**) (0.631 g, 57%) as a yellow oil. Spectroscopic data was as described above.

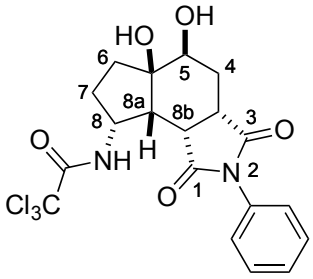
(3a*S,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-Hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (236)[99]**



To a solution of (3a*S**,8*R**,8a*S**,8b*R**)-5-(benzyldimethylsilyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**235**) (0.038 g, 0.066 mmol) in tetrahydrofuran (1 mL) was added methanol (2 mL) and 6 M hydrochloric acid (3 mL). The reaction mixture was stirred at 60 °C for 18 h. A 20% solution of aqueous sodium carbonate (6 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3)

gave (3a*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**236**) (0.021 g, 74%) as a white solid. Mp 174–176 °C; Spectroscopic data was consistent with the literature.[99] δ_H (500 MHz, $CDCl_3$) 1.81 (1H, qd, *J* 12.5, 7.6 Hz, 7-*H*H), 2.10–2.18 (1H, m, 7-H*H*), 2.19–2.38 (2H, m, 6-*H*H and 4-*H*H), 2.47 (1H, dd, *J* 16.2, 7.6 Hz, 6-H*H*), 2.85 (1H, ddd, *J* 15.1, 7.2, 1.1 Hz, 4-H*H*), 2.89–2.96 (1H, m, 8a-H), 3.33 (1H, ddd, *J* 8.7, 7.2, 1.1 Hz, 3a-H), 3.43 (1H, dd, *J* 8.7, 6.4 Hz, 8b-H), 4.80–4.91 (1H, m, 8-H), 5.75–5.81 (1H, m, 5-H), 7.15–7.20 (2H, m, 2 × ArH), 7.39–7.51 (3H, m, 3 × ArH), 8.95 (1H, d, *J* 9.2 Hz, NH); δ_C (126 MHz, $CDCl_3$) 26.1 (CH_2), 28.6 (CH_2), 31.7 (CH_2), 39.4 (CH), 41.2 (CH), 41.5 (CH), 52.9 (CH), 92.9 (C), 117.1 (CH), 126.5 (2 × CH), 129.2 (CH), 129.3 (2 × CH), 131.5 (C), 145.8 (C), 162.3 (C), 178.6 (C), 179.7 (C); *m/z* (ESI) 449 (MNa^+. 100%).

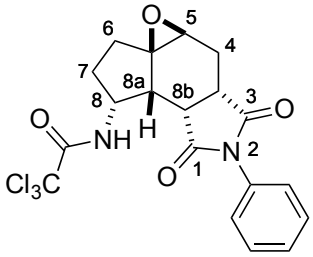
(3a*S*,5S*,5*a*R,8*R**,8a*R**,8b*R**)-5,5a-Dihydroxy-2-phenyl-3a,4,5,5a,6,7,8a,8b-octahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (237).**



(3a*S*,5S*,5*a*R**,8*R**,8a*R**,8b*R**)-5,5a-Dihydroxy-2-phenyl-3a,4,5,5a,6,7,8a,8b-octahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**237**) was synthesised as described for (3a*S*,5R*,5*a*R**,8*R**,8a*R**,8b*R**)-5,5a-dihydroxy-2,5-diphenyl-3a,4,5,5a,6,7,8a,8b-octahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**216**) using (3a*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-Hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**236**) (0.029 g, 0.068 mmol). Purification by flash column chromatography (dichloromethane/methanol, 19:1) gave (3a*S*,5S*,5*a*R**,8*R**,8a*R**,8b*R**)-5,5a-dihydroxy-2-phenyl-3a,4,5,5a,6,7,8a,8b-octahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-

1,3(2*H*,3a*H*)-dione (**237**) (0.027 g, 86%) as a white solid. Mp 168–170 °C; ν_{max}/cm^{-1} (neat) 3471 (OH), 3329 (NH), 2946 (CH), 1698 (C=O), 1515 (C=C), 1386, 1175, 821, 754; δ_H (500 MHz, $CDCl_3$) 1.61–1.76 (1H, m, 6-*H*H), 1.85–2.03 (2H, m, 6-H*H* and 7-*H*H), 2.09 (1H, dt, *J* 13.5, 3.7 Hz, 4-*H*H), 2.18 (1H, ddd, *J* 13.5, 10.8, 6.7 Hz, 4-H*H*), 2.41–2.55 (1H, m, 7-H*H*), 2.70–2.89 (2H, m, 8a-H and OH), 3.00 (1H, br s, OH), 3.22 (1H, dd, *J* 9.0, 7.1 Hz, 8b-H), 3.35 (1H, ddd, *J* 9.0, 6.7, 3.7 Hz, 3a-H), 3.62 (1H, d, *J* 10.8 Hz, 5-H), 5.04–5.16 (1H, m, 8-H), 7.21–7.25 (2H, m, 2 × ArH), 7.40–7.56 (3H, m, 3 × ArH), 8.56 (1H, d, *J* 9.5 Hz, NH); δ_C (126 MHz, $CDCl_3$) 29.7 (CH_2), 30.3 (CH_2), 37.1 (CH_2), 38.6 (CH), 39.3 (CH), 48.1 (CH), 51.9 (CH), 70.1 (CH), 81.9 (C), 92.8 (C), 126.3 (2 × CH), 129.2 (CH), 129.5 (2 × CH), 131.2 (C), 162.1 (C), 178.0 (C), 178.8 (C); *m/z* (ESI) 483.0242 (MNa^+. $C_{19}H_{19}{}^{35}Cl_3N_2NaO_5$ requires 483.0252).

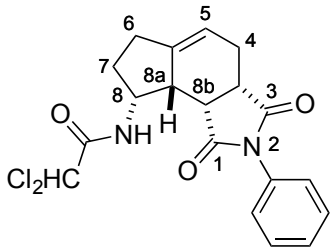
(3a*S*,5S*,5*a*R,8*R**,8a*R**,8b*R**)-5,5a-Epoxy-3a,4,5,5a,6,7,8a,8b-octahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (238)**



(3a*S*,5S*,5*a*R**,8*R**,8a*R**,8b*R**)-5,5a-Epoxy-3a,4,5,5a,6,7,8a,8b-octahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**238**) was synthesised as described for (3a*S*,5R*,5*a*R**,8*R**,8a*R**,8b*R**)-5,5a-epoxy-2,5-diphenyl-3a,4,5,5a,6,7,8a,8b-octahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**217**) using (3a*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**236**) (0.032 g, 0.075 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave (3a*S*,5S*,5*a*R**,8*R**,8a*R**,8b*R**)-5,5a-epoxy-3a,4,5,5a,6,7,8a,8b-octahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**238**)

(0.024 g, 73%) as a light brown solid. Mp 154–156 °C; ν_{max}/cm^{-1} (neat) 3265 (NH), 2934 (CH), 1697 (C=O), 1520 (C=C), 1394, 1192, 824, 773; δ_H (500 MHz, $CDCl_3$) 1.65−1.72 (1H, m, 6-*H*H), 1.94−2.11 (2H, m, 6-H*H* and 7-*H*H), 2.23 (1H, dd, *J* 15.5, 8.5 Hz, 4-*H*H), 2.26−2.34 (1H, m, 7-H*H*), 2.77 (1H, dd, *J* 15.5, 4.1 Hz, 4-H*H*), 2.96 (1H, dd, *J* 11.2, 5.0 Hz, 8a-H), 3.05−3.12 (1H, m, 3a-H), 3.17 (1H, dd, *J* 9.8, 5.0 Hz, 8b-H), 3.59 (1H, d, *J* 4.1 Hz, 5-H), 4.70−4.82 (1H, m, 8-H), 7.27−7.33 (2H, m, 2 × ArH), 7.38−7.53 (3H, m, 3 × ArH), 9.33 (1H, d, *J* 9.8 Hz, NH); δ_C (126 MHz, $CDCl_3$) 25.6 (CH_2), 29.1 (CH_2), 32.8 (CH_2), 38.4 (CH), 40.0 (CH), 40.5 (CH), 50.5 (CH), 56.5 (CH), 67.9 (C), 92.8 (C), 126.7 (2 × CH), 128.9 (CH), 129.3 (2 × CH), 132.3 (C), 162.5 (C), 178.9 (C), 180.3 (C); *m/z* (ESI) 465.0144 (MNa^+. $C_{19}H_{17}{}^{35}Cl_3N_2NaO_4$ requires 465.0146).

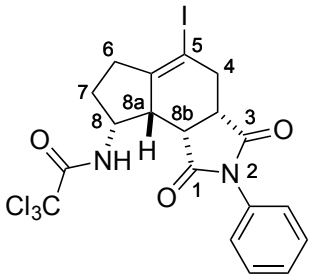
(3a*S,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-Hexahydro-2-phenyl-8-(2′,2′-dichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (239)**



(3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-Hexahydro-2-phenyl-8-(2′,2′-dichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**239**) was synthesised as described for (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2′,2′-dichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**214**) using (3a*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**236**) (0.027 g, 0.063 mmol). The mixture was stirred under an atmosphere of hydrogen at room temperature for 18 h. The reaction mixture was filtered through a short pad of Celite® with diethyl ether (50 mL) and the solvent was removed *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2′,2′-dichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**239**) (0.021 g, 85%) as a white solid. Mp 142–144 °C; ν_{max}/cm^{-1} (neat) 3327 (NH), 2963 (CH), 1694 (C=O), 1524 (C=C), 1499, 1389, 1201, 1184, 767,

753; δ_H (500 MHz, $CDCl_3$) 1.74–1.85 (1H, m, 7-*H*H), 2.09 (1H, dt, *J* 12.1, 7.1 Hz 7-H*H*), 2.19–2.35 (2H, m, 4-*H*H and 6-*H*H), 2.45 (1H, dd, *J* 16.1, 7.7 Hz, 6-H*H*), 2.81–2.92 (2H, m, 4-H*H* and 8a-H), 3.31 (1H, td, *J* 8.8, 1.2 Hz, 3a-H), 3.42 (1H, dd, *J* 8.8, 6.4 Hz, 8b-H), 4.82–4.92 (1H, m, 8-H), 5.74–5.79 (1H, m, 5-H), 5.96 (1H, s, $CHCl_2$), 7.16–7.20 (2H, m, 2 × ArH), 7.39–7.51 (3H, m, 3 × ArH), 8.64 (1H, d, *J* 9.5 Hz, NH); δ_C (126 MHz, $CDCl_3$) 26.2 (CH_2), 28.6 (CH_2), 31.7 (CH_2), 39.4 (CH), 41.2 (CH), 41.5 (CH), 51.6 (CH), 66.7 (CH), 116.9 (CH), 126.5 (2 × CH), 129.0 (CH), 129.3 (2 × CH), 131.6 (C), 146.0 (C), 164.5 (C), 178.6 (C), 179.6 (C); *m/z* (ESI) 415.0582 (MNa^+. $C_{19}H_{18}{}^{35}Cl_2N_2NaO_3$ requires 415.0587).

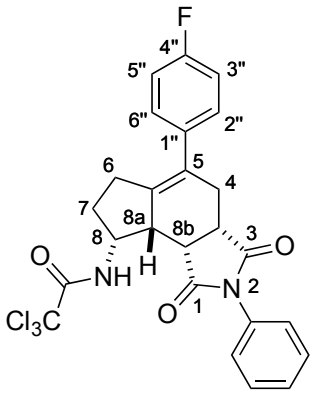
(3a*S,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-Hexahydro-5-iodo-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (240)**



To a solution of (3a*S**,8*R**,8a*S**,8b*R**)-5-(benzyldimethylsilyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**235**) (0.470 g, 0.820 mmol) in dichloromethane (10 mL) at −78 °C was added iodine monochloride (0.0570 mL, 1.14 mmol). The reaction mixture was stirred at −78 °C for 3 h, then the excess iodine monochloride was destroyed by adding a 10% solution of sodium thiosulfate (20 mL) and the mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-iodo-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**240**) (0.400 g, 88%) as a white solid. Mp 130−132 °C; ν_{max}/cm^{-1} (neat) 3309 (NH), 2954 (CH), 1698 (C=O), 1517 (C=C), 1391, 1200, 823; δ_H (400 MHz, $CDCl_3$) 1.86 (1H, qd, *J* 12.3, 8.2 Hz, 7-*H*H), 2.12–2.34 (2H, m, 6-*H*H and 7-H*H*), 2.46 (1H, dd, *J* 16.9, 8.2 Hz, 6-H*H*), 2.84–2.94 (1H, m, 4-*H*H), 3.02–3.08 (1H, m, 8a-H), 3.28 (1H,

dd, *J* 15.7, 1.2 Hz, 4-H*H*), 3.37 (1H, ddd, *J* 8.6, 6.7, 1.2 Hz, 3a-H), 3.42 (1H, dd, *J* 8.6, 5.8 Hz, 8b-H), 4.86–4.99 (1H, m, 8-H), 7.16–7.21 (2H, m, 2 × ArH), 7.41–7.53 (3H, m, 3 × ArH), 8.84 (1H, d, *J* 9.6 Hz, NH); δ_C (101 MHz, $CDCl_3$) 30.6 (CH_2), 33.6 (CH_2), 39.8 (CH_2), 40.6 (CH), 41.1 (CH), 44.5 (CH), 53.9 (CH), 82.0 (C), 92.8 (C), 126.5 (2 × CH), 129.3 (CH), 129.4 (2 × CH), 131.4 (C), 151.0 (C), 162.1 (C), 177.0 (C), 178.9 (C); *m/z* (ESI) 574.9151 (MNa^+. $C_{19}H_{16}{}^{35}Cl_3IN_2NaO_3$ requires 574.9163).

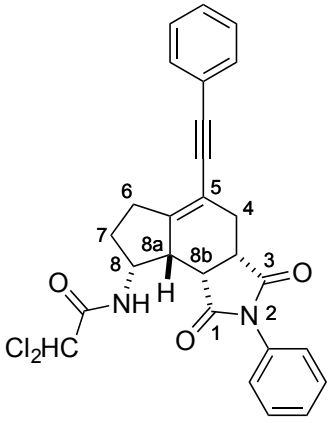
(3a*S,8*R**,8a*S**,8b*R**)-5-(4''-Fluorophenyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (241).**



(3a*S**,8*R**,8a*S**,8b*R**)-5-(4''-Fluorophenyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**241**) was synthesised as described for 3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-3a,4,6,7,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**201**) (Method B) using (3aS*,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-iodo-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**240**) (0.030 g, 0.054 mmol) and 4-fluorophenylboronic acid (0.019 g, 0.14 mmol) and performed at 70 °C for 12 h. Flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave (3a*S**,8*R**,8a*S**,8b*R**)-5-(4''-fluorophenyl)-3a,4,6,7,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**241**) (0.013 g, 46%) as a white solid. Mp 124–126 °C; ν_{max}/cm^{-1} (neat) 3312 (NH), 2926 (CH), 1700 (C=O), 1510 (C=C), 1500, 1391, 838, 756; δ_H (500 MHz, $CDCl_3$) 1.69–

1.82 (1H, m, 7-*H*H), 2.12–2.20 (1H, m, 7-H*H*), 2.48–2.66 (3H, m, 4-*H*H and 6-H_2), 3.12 (1H, dd, *J* 8.6, 6.6 Hz, 8a-H), 3.25 (1H, dd, *J* 15.2, 1.2 Hz, 4-H*H*), 3.45–3.56 (2H, m, 3a-H and 8b-H), 4.88–4.98 (1H, m, 8-H), 7.00–7.09 (4H, m, 3"-H, 5"-H and 2 × ArH), 7.19–7.25 (2H, m, 2"-H and 6"-H), 7.37–7.48 (3H, m, 3 × ArH), 8.95 (1H, d, *J* 9.6 Hz, NH); δ_C (126 MHz, $CDCl_3$) 28.3 (CH_2), 31.7 (CH_2), 31.7 (CH_2), 40.3 (CH), 41.6 (CH), 43.8 (CH), 52.8 (CH), 92.9 (C), 115.4 (2 × CH, $^2J_{CF}$ 21.4 Hz), 126.5 (2 × CH), 129.2 (2 × CH, $^3J_{CF}$ 8.0 Hz), 129.2 (CH), 129.4 (2 × CH), 129.4 (C), 131.4 (C), 134.9 (C, $^4J_{CF}$ 3.2 Hz), 139.6 (C), 161.8 (C, $^1J_{CF}$ 247.3 Hz), 162.3 (C), 178.5 (C), 179.7 (C); *m/z* (ESI) 543.0393 (MNa^+. $C_{25}H_{20}F^{35}Cl_3N_2NaO_3$ requires 543.0416).

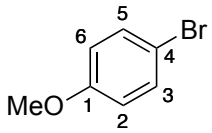
(3a*S,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-Hexahydro-5-(phenylethynyl)-2-phenyl-8-(2',2'-dichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (243)**



To a solution of (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-iodo-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**240**) (0.016 g, 0.029 mmol) in *N*,*N*-dimethylformamide (0.5 mL) were added copper iodide (0.001 g, 0.006 mmol) and bis(triphenylphosphine)palladium dichloride (0.002 g, 0.003 mmol). Phenylacetylene (**242**) (0.004 mL, 0.037 mmol) was dissolved in degassed triethylamine (2 mL) and added to the reaction mixture. The solution was briefly heated to 60 °C and then left to stir at room temperature for 3 h. The solution was concentrated *in vacuo* and purified by flash column chromatography (petroleum ether/ethyl acetate, 3:2) to give (3a*S**,8*R**,8a*S**,8b*R**)-3a,4,6,7,8a,8b-hexahydro-5-(phenylethynyl)-2-phenyl-8-

(2',2'-dichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**243**) (0.007 g, 48%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3021 (CH), 2361, 1705 (C=O), 1522 (C=C), 1393, 1215, 754; δ_H (400 MHz, $CDCl_3$) 1.78–1.92 (1H, m, 7-*H*H), 2.09–2.22 (1H, m, 7-H*H*), 2.35–2.57 (2H, m, 4-*H*H and 6-*H*H), 2.84 (1H, dd, *J* 17.6, 7.7 Hz, 6-H*H*), 2.99–3.02 (1H, m, 8a-H), 3.06 (1H, dd, *J* 15.0, 1.3 Hz, 4-H*H*), 3.39 (1H, ddd, *J* 8.8, 7.7, 1.3 Hz, 3a-H), 3.47 (1H, dd, *J* 8.8, 6.3 Hz, 8b-H), 4.94 (1H, dtd, *J* 12.3, 9.8, 7.1 Hz, 8-H), 5.97 (1H, s, $CHCl_2$), 7.18–7.23 (2H, m, 2 × ArH), 7.29–7.34 (3H, m, 3 × ArH), 7.38–7.53 (5H, m, 5 × ArH), 8.58 (1H, d, *J* 9.8 Hz, NH); δ_C (101 MHz, $CDCl_3$) 28.7 (CH_2), 31.0 (CH_2), 31.3 (CH_2), 39.4 (CH), 41.1 (CH), 42.8 (CH), 51.7 (CH), 66.6 (CH), 86.7 (C), 93.5 (C), 111.8 (C), 123.0 (C), 126.5 (2 × CH), 128.3 (2 × CH), 128.4 (CH), 129.1 (CH), 129.3 (2 × CH), 131.5 (2 × CH), 131.5 (C), 151.4 (C), 164.5 (C), 177.7 (C), 179.0 (C); *m/z* (ESI) 515.0875 (MNa^+. $C_{27}H_{22}{}^{35}Cl_2N_2NaO_3$ requires 515.0900).

4-Bromoanisole (250a)[206]

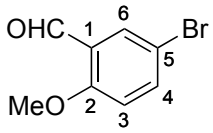


Method A- *N*-Bromosuccinimide (165 mg, 0.930 mmol) was added to a solution of iron(III) chloride (7.50 mg, 0.0460 mmol) in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide ([BMIM]NTf_2) (0.30 mL) under an atmosphere of air. The mixture was stirred at room temperature for 0.5 h before anisole (101 µL, 0.930 mmol) in [BMIM]NTf_2 (0.10 mL) was added. The reaction mixture was heated to 40 °C for 1.5 h. The reaction progress was monitored by ^{1}H NMR spectroscopy. The reaction mixture was extracted into 5% ethyl acetate in hexane (3 × 50 mL) using sonication in a water bath for 0.1 h. The suspension was washed with an aqueous solution of 1 M sodium thiosulfate (10 mL), brine (10 mL), dried ($MgSO_4$) and then filtered through a pad of Celite®. The solvent was removed under reduced pressure. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 4-bromoanisole (**250a**) (141 mg, 82%) as a pale yellow oil. Spectroscopic data was consistent with the literature.[206] δ_H (400 MHz, $CDCl_3$) 3.78 (3H, s, OCH_3), 6.76–6.81 (2H, m, 2-H and 6-H), 7.35–7.40 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 55.4 (CH_3), 112.8 (C), 115.8 (2 × CH),

132.3 (2 × CH), 158.7 (C); *m/z* (EI) 186 (M^+. 100%), 171 (35), 143 (28).

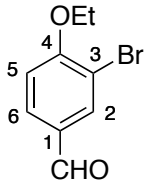
Method B- Iron(III) trichloride (4.00 mg, 0.0250 mmol) was dissolved in [BMIM]NTf_2 (22.0 µL, 0.0750 mmol), pre-stirred for 0.5 h at room temperature and then added to a solution of *N*-bromosuccinimide (178 mg, 1.00 mmol) in toluene (1.0 mL). Anisole (108 µL, 1.00 mmol) was then added and the mixture was stirred at 40 °C for 4 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M sodium thiosulfate solution (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 4-bromoanisole (**250a**) (149 mg, 79%) as a pale yellow oil. Spectroscopic data was as described above.

5-Bromo-2-methoxybenzaldehyde (250b)[207]



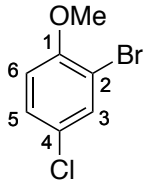
5-Bromo-2-methoxybenzaldehyde (**250b**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 2-methoxybenzaldehyde (60 mg, 0.44 mmol) and performing the reaction at 40 °C for 1.5 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 5-bromo-2-methoxybenzaldehyde (**250b**) (83 mg, 88%) as a white solid. Mp 112–114 °C (lit.[207] 116–117 °C); δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, OCH_3), 6.90 (1H, d, *J* 8.9 Hz, 3-H), 7.64 (1H, dd, *J* 8.9, 2.6 Hz, 4-H), 7.92 (1H, d, *J* 2.6 Hz, 6-H), 10.39 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 56.0 (CH_3), 113.5 (C), 113.7 (CH), 126.1 (C), 131.1 (CH), 138.3 (CH), 160.7 (C), 188.3 (CH); *m/z* (EI) 214 (M^+. 100%), 170 (30), 143 (20), 135 (8), 118 (24), 92 (10), 75 (27), 63 (30), 50 (12).

3-Bromo-4-ethoxybenzaldehyde (250c)



3-Bromo-4-ethoxybenzaldehyde (**250c**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 4-ethoxybenzaldehyde (130 mg, 0.850 mmol) and performing the reaction at 40 °C for 22 h. Purification by flash column chromatography (petroleum ether/diethyl ether, 19:1) gave 3-bromo-4-ethoxybenzaldehyde (**250c**) (172 mg, 88%) as a white solid. Mp 70–72 °C; ν_{max}/cm^{-1} (neat) 2977 (CH), 1684 (CO), 1595 (C=C), 1493, 1287, 1049, 813, 667; δ_H (500 MHz, $CDCl_3$) 1.48 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 4.15 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 6.93 (1H, d, *J* 8.5 Hz, 5-H), 7.74 (1H, dd, *J* 8.5, 2.0 Hz, 6-H), 8.02 (1H, d, *J* 2.0 Hz, 2-H), 9.78 (1H, s, CHO); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 65.2 (CH_2), 112.3 (CH), 112.8 (C), 130.4 (C), 131.2 (CH), 134.5 (CH), 160.1 (C), 189.6 (CH); *m/z* (ESI) 250.9667 (MNa^+. $C_9H_9{}^{79}BrNaO_2$ requires 250.9678).

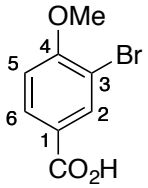
2-Bromo-4-chloroanisole (250d)[208]



Method A- 2-Bromo-4-chloroanisole (**250d**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 4-chloroanisole (62 µL, 0.50 mmol) and performing the reaction at 40 °C for 1 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 17:3) gave 2-bromo-4-chloroanisole (**250d**) (109 mg, 99%) as a colourless oil. Spectroscopic data was consistent with the literature.[208] δ_H (500 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 6.82 (1H, d, *J* 8.8 Hz, 6-H), 7.24 (1H, dd, *J* 8.8, 2.5 Hz, 5-H), 7.54 (1H, d, *J* 2.5 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 56.6 (CH_3), 112.3 (C), 112.7 (CH), 126.1 (C), 128.4 (CH), 132.9 (CH), 154.9 (C); *m/z* (EI) 222 (M^+. 100%), 207 (50), 179 (36), 126 (10), 75 (12), 63 (21).

Method B- *N*-Chlorosuccinimide (140 mg, 1.05 mmol) was added to a solution of iron(III) chloride (8.00 mg, 0.0500 mmol) in [BMIM]NTf_2 ((0.30 mL) under an atmosphere of air. The mixture was stirred at room temperature for 0.5 h before anisole (108 µL, 1.00 mmol) was added. The mixture was stirred at 60 °C for 6 h. The reaction mixture was cooled to room temperature and *N*-bromosuccinimide (178 mg, 1.00 mmol) was then added. The reaction mixture was heated to 40 °C for 18 h. The reaction mixture was then extracted with 5% ethyl acetate in hexane (3 × 50 mL) using sonication in a water bath for 0.1 h. The suspension was washed with an aqueous solution of 1 M sodium thiosulfate (10 mL), brine (10 mL), dried ($MgSO_4$) and then filtered through a pad of Celite®. The solvent was removed under reduced pressure. Purification by flash column chromatography (petroleum ether/ethyl acetate, 17:3) gave 2-bromo-4-chloroanisole (**250d**) (178 mg, 81%) as a colourless oil. Spectroscopic data was as described above.

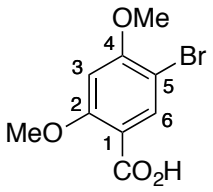
3-Bromo-4-methoxybenzoic acid (250e)[209]



N-Bromosuccinimide (89 mg, 0.50 mmol) was added to a solution of iron(III) chloride (4.0 mg, 0.025 mmol) in [BMIM]NTf_2 (0.15 mL) under an atmosphere of air. The mixture was stirred at room temperature for 0.5 h before 4-methoxybenzoic acid (76 mg, 0.50 mmol) in [BMIM]NTf_2 (0.10 mL) was added. The reaction mixture was heated to 40 °C for 4 h. The reaction mixture was diluted with dichloromethane (20 mL) and extracted with an aqueous solution of 1 M sodium hydroxide (10 mL). The aqueous phase was separated and then acidified with 1 M hydrochloric acid (10 mL), and extracted into dichloromethane (2 × 50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (dichloromethane/methanol, 19:1) gave 3-bromo-4-methoxybenzoic acid (**250e**) (96 mg, 83%) as a white solid. Mp 206–208 °C (lit.[209] 201–206 °C); δ_H (500 MHz, $CDCl_3$) 3.98 (3H, s, OCH_3), 6.95 (1H, d, *J* 8.7 Hz, 5-H), 8.06 (1H, dd, *J* 8.7, 2.1 Hz, 6-H), 8.30 (1H, d, *J* 2.1 Hz, 2-H); δ_C (126 MHz, $CDCl_3$) 56.5 (CH_3), 111.1 (CH), 111.6 (C), 122.7 (C), 131.4 (CH),

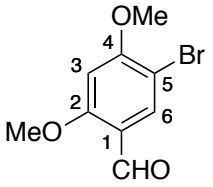
135.5 (CH), 160.2 (C), 169.8 (C); *m/z* (ESI) 255 (MNa^+. 100%).

5-Bromo-2,4-dimethoxybenzoic acid (250f)[210]



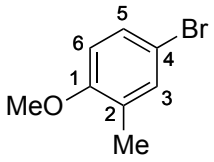
5-Bromo-2,4-dimethoxybenzoic acid (**250f**) was synthesised as described for 3-bromo-4-methoxybenzoic acid (**250e**) using 2,4-dimethoxybenzoic acid (91 mg, 0.50 mmol) and performing the reaction at 40 °C for 4 h. Purification by flash column chromatography (dichloromethane/methanol, 19:1) gave 2,4-dimethoxy-5-bromobenzoic acid (**250f**) (85 mg, 65%) as a white solid. Mp 190–192 °C (lit.[210] 192–194 °C); δ_H (400 MHz, $CDCl_3$) 3.99 (3H, s, OCH_3), 4.09 (3H, s, OCH_3), 6.51 (1H, s, 3-H), 8.33 (1H, s, 6-H), 10.38 (1H, s, CO_2H); δ_C (101 MHz, $CDCl_3$) 56.6 (CH_3), 57.0 (CH_3), 95.8 (CH), 104.4 (C), 111.2 (C), 137.8 (CH), 159.0 (C), 160.9 (C), 164.1 (C); *m/z* (ESI) 283 (MNa^+. 100%).

5-Bromo-2,4-dimethoxybenzaldehyde (250g)[211]



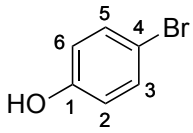
5-Bromo-2,4-dimethoxybenzaldehyde (**250g**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 2,4-dimethoxybenzaldehyde (80 mg, 0.50 mmol) and performing the reaction at 20 °C for 2.5 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 5:1) gave 5-bromo-2,4-dimethoxybenzaldehyde (**250g**) (115 mg, 94%) as a white solid. Mp 134–136 °C (lit.[211] 139–140 °C); δ_H (500 MHz, $CDCl_3$) 3.93 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 6.42 (1H, s, 3-H), 7.96 (1H, s, 6-H), 10.20 (1H, s, CHO); δ_C (126 MHz, $CDCl_3$) 56.0 (CH_3), 56.5 (CH_3), 95.6 (CH), 103.5 (C), 119.4 (C), 132.8 (CH), 161.7 (C), 163.0 (C), 187.1 (CH); *m/z* (ESI) 267 (MNa^+. 100%).

4-Bromo-2-methylanisole (250h)[212]



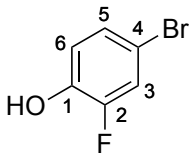
4-Bromo-2-methylanisole (**250h**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 2-methylanisole (62 μL, 0.50 mmol) and performing the reaction at 40 °C for 2 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 4-bromo-2-methylanisole (**250h**) (90 mg, 90%) as a light yellow solid. Mp 64–66 °C (lit.[212] 66–68 °C); δ_H (500 MHz, $CDCl_3$) 2.21 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 6.70 (1H, d, *J* 9.0 Hz, 6-H), 7.24–7.30 (2H, m, 3-H and 5-H); δ_C (126 MHz, $CDCl_3$) 16.0 (CH_3), 55.5 (CH_3), 111.5 (CH), 112.4 (C), 129.0 (C), 129.4 (CH), 133.2 (CH), 156.9 (C); *m/z* (EI) 200 (M^+. 100%), 185 (47), 149 (27), 111 (36), 97 (49), 85 (54), 78 (35), 71 (69), 57 (100).

4-Bromophenol (250i)[213]



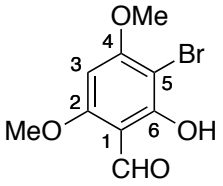
5-Bromophenol (**250i**) was synthesised as described for 3-bromo-4-methoxybenzoic acid (**250e**) using phenol (47 mg, 0.50 mmol) and performing the reaction at 20 °C for 0.5 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 4-bromophenol (**250i**) (82 mg, 93%) as a white solid. Mp 58–60 °C (lit.[213] 56–59 °C); δ_H (400 MHz, $CDCl_3$) 5.03 (1H, br s, OH), 6.70–6.75 (2H, m, 2-H and 6-H), 7.31–7.36 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 113.0 (C), 117.2 (2 × CH), 132.5 (2 × CH), 154.6 (C); *m/z* (ESI) 173 ($[M–H]^-$. 100%).

4-Bromo-2-fluorophenol (250j)[214]



4-Bromo-2-fluorophenol (**250j**) was synthesised as described for 3-bromo-4-methoxybenzoic acid (**250e**) using 2-fluorophenol (44 μL, 0.50 mmol) and performing the reaction at 40 °C for 2 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 4-bromo-2-fluorophenol (**250j**) (77 mg, 82%) as a colourless oil. Spectroscopic data was consistent with the literature.[214] δ_H (500 MHz, $CDCl_3$) 5.07 (1H, d, *J* 4.2 Hz, OH), 6.90 (1H, dd, *J* 9.0, 8.8 Hz, 6-H), 7.16 (1H, ddd, *J* 8.8, 2.2, 1.6 Hz, 5-H), 7.24 (1H, dd, *J* 9.9, 2.2 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 111.7 (C, d, $^3J_{CF}$ 8.2 Hz), 118.7 (CH, d, $^4J_{CF}$ 2.2 Hz), 119.2 (CH, d, $^2J_{CF}$ 21.1 Hz), 128.1 (CH, d, $^3J_{CF}$ 3.8 Hz), 143.0 (C, d, $^2J_{CF}$ 14.1 Hz), 151.0 (C, d, $^1J_{CF}$ 241.8 Hz); *m/z* (EI) 190 (M^+. 100%), 161 (4), 142 (9), 111 (6), 83 (29), 63 (38), 57 (19).

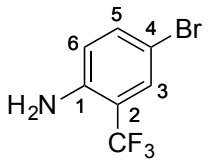
5-Bromo-2,4-dimethoxy-6-hydroxybenzaldehyde (250k)



5-Bromo-2,4-dimethoxy-6-hydroxybenzaldehyde (**250k**) was synthesised as described for 3-bromo-4-methoxybenzoic acid (**250e**) using 2,4-dimethoxy-6-hydroxybenzaldehyde (92 mg, 0.50 mmol) and performing the reaction at 20 °C for 6 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 5-bromo-2,4-dimethoxy-6-hydroxybenzaldehyde (**250k**) (97 mg, 74%) as a white solid. Mp 188–190 °C; ν_{max}/cm^{-1} (neat) 2924 (CH), 1636 (CO), 1615 (C=C), 1470, 1450, 1427, 1406, 1283, 1233, 1217, 1124, 1089, 981, 772, 723; δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.01 (1H, s, 3-H), 10.08 (1H, s, CHO), 12.96 (1H, s, OH); δ_C (101 MHz, $CDCl_3$) 56.0 (CH_3), 56.6 (CH_3), 86.9 (CH), 90.8 (C), 106.4 (C), 161.4 (C), 163.4 (C), 163.8 (C), 191.8 (C); *m/z*

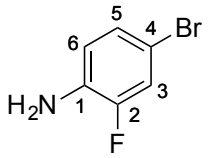
(ESI) 282.9575 (MNa^+. $C_9H_9{}^{79}BrNaO_4$ requires 282.9576).

4-Bromo-2-trifluoromethylaniline (250l)[215]



4-Bromo-2-trifluoromethylaniline (**250l**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 2-trifluoromethylaniline (63 µL, 0.50 mmol) and performing the reaction at 40 °C for 2 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 4-bromo-2-trifluoromethylaniline (**250l**) (0.12 g, 99%) as a colourless oil. Spectroscopic data was consistent with the literature.[215] δ_H (500 MHz, $CDCl_3$) 4.18 (2H, s, NH_2), 6.62 (1H, d, *J* 8.7 Hz, 6-H), 7.37 (1H, dd, *J* 8.7, 2.2 Hz, 5-H), 7.53 (1H, d, *J* 2.2 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 109.1 (C), 115.3 (C, q, $^2J_{CF}$ 30.7 Hz), 118.9 (CH), 124.1 (C, q, $^1J_{CF}$ 272.6 Hz), 129.3 (CH, q, $^3J_{CF}$ 5.4 Hz), 135.8 (CH), 143.6 (C); *m/z* (EI) 239 (M^+. 100%), 219 (51), 192 (37), 160 (8), 140 (12), 132 (11), 113 (15), 70 (14), 63 (19).

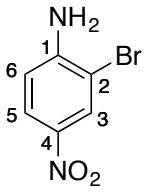
4-Bromo-2-fluoroaniline (250m)[216]



4-Bromo-2-fluoroaniline (**250m**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 2-fluoroaniline (56 mg, 0.50 mmol) and performing the reaction at 20 °C for 1.5 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-bromo-2-fluoroaniline (**250m**) (70 mg, 73%) as a light brown oil. Spectroscopic data was consistent with the literature.[216] δ_H (500 MHz, $CDCl_3$) 3.72 (2H, s, NH_2), 6.65 (1H, dd, *J* 9.4, 8.5 Hz, 6-H), 7.05 (1H, ddd, *J* 8.5, 2.2, 1.1 Hz, 5-H), 7.14 (1H, dd, *J* 10.5, 2.2 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 108.9 (C, d, $^3J_{CF}$ 8.8 Hz), 117.8 (CH, d, $^3J_{CF}$ 4.3 Hz), 118.7 (CH, d, $^2J_{CF}$ 21.9 Hz), 127.4 (CH, d, $^4J_{CF}$ 3.6 Hz), 133.8 (C, d, $^2J_{CF}$ 12.8 Hz), 151.4 (C, d, $^1J_{CF}$

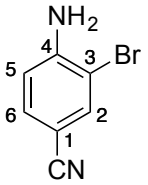
243.4 Hz); *m/z* (EI) 189 (M^+. 100%), 110 (21), 83 (27), 63 (11).

2-Bromo-4-nitroaniline (250n)[217]



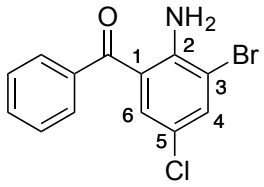
2-Bromo-4-nitroaniline (**250n**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 4-nitroaniline (69 mg, 0.50 mmol) and performing the reaction at 40 °C for 2 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 2-bromo-4-nitroaniline (**250n**) (87 mg, 80%) as a yellow solid. Mp 104–106 °C (lit.[217] 103–104 °C); δ_H (500 MHz, $CDCl_3$) 4.89 (2H, s, NH_2), 6.77 (1H, d, *J* 8.9 Hz, 6-H), 8.04 (1H, dd, *J* 8.9, 2.4 Hz, 5-H), 8.38 (1H, d, *J* 2.4 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 107.1 (C), 113.6 (CH), 125.0 (CH), 129.3 (CH), 139.1 (C), 150.0 (C); *m/z* (ESI) 239 (MNa^+. 99%), 227 (4), 200 (10).

4-Amino-3-bromobenzonitrile (250o)[218]



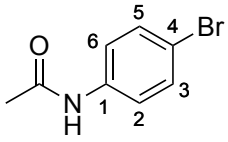
4-Amino-3-bromobenzonitrile (**250o**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 4-cyanoaniline (59 mg, 0.50 mmol) and performing the reaction at 40 °C for 22 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 4-amino-3-bromobenzonitrile (**250o**) (58 mg, 59%) as a white solid. Mp 110–112 °C (lit.[218] 110–112 °C); δ_H (400 MHz, $CDCl_3$) 4.64 (2H, s, NH_2), 6.74 (1H, d, *J* 8.4 Hz, 6-H), 7.37 (1H, dd, *J* 8.4, 1.8 Hz, 5-H), 7.68 (1H, d, *J* 1.8 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 101.5 (C), 108.0 (C), 114.9 (CH), 118.7 (C), 132.6 (CH), 136.6 (CH), 148.2 (C); *m/z* (ESI) 221 (MNa^+. 100%), 199 (26), 171 (3).

2-Amino-3-bromo-5-chlorobenzophenone (250p)[219]



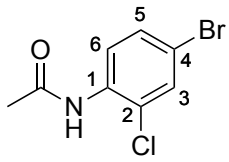
2-Amino-3-bromo-5-chlorobenzophenone (**250p**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 2-amino-5-chlorobenzophenone (120 mg, 0.500 mmol) and performing the reaction at 70 °C for 1 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 2-amino-3-bromo-5-chlorobenzophenone (**250p**) (140 mg, 90%) as a yellow solid. Mp 101–102 °C (lit.[219] 102–103 °C); δ_H (500 MHz, $CDCl_3$) 6.60 (2H, s, NH_2), 7.41 (1H, d, *J* 2.4 Hz, 6-H) 7.46–7.52 (2H, m, 2 × ArH), 7.55–7.65 (4H, m, 4 × ArH); δ_C (126 MHz, $CDCl_3$) 111.4 (C), 119.4 (C), 119.7 (C), 128.5 (2 × CH), 129.3 (2 × CH), 132.0 (CH), 132.9 (CH), 136.6 (CH), 138.9 (C), 146.6 (C), 197.5 (C); *m/z* (ESI) 334 (MNa^+. 100%).

4-Bromoacetanilide (250q)[220]



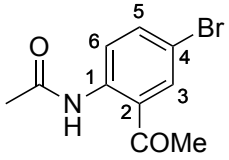
4-Bromoacetanilide (**250q**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using acetanilide (68 mg, 0.50 mmol) and performing the reaction at 40 °C for 2.5 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 4-bromoacetanilide (**250q**) (0.10 g, 96%) as a white solid. Mp 162–164 °C (lit.[220] 164–166 °C); δ_H (500 MHz, $CDCl_3$) 2.17 (3H, s, CH_3), 7.30 (1H, br s, NH), 7.37–7.44 (4H, m, 2-H, 3-H, 5-H and 6-H); δ_C (126 MHz, $CDCl_3$) 24.6 (CH_3), 116.9 (C), 121.4 (2 × CH), 132.0 (2 × CH), 136.9 (C), 168.3 (C); *m/z* (ESI) 236 (MNa^+. 100%).

***N*-(4-Bromo-2-chlorophenyl)acetamide (250r)**[221]



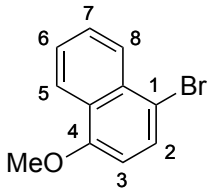
N-(4-Bromo-2-chlorophenyl)acetamide (**250r**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using *N*-(2-chlorophenyl)acetamide (85 mg, 0.50 mmol) in a co-solvent system of [BMIM]NTf_2 (0.3 mL) and toluene (0.1 mL) and performing the reaction at 40 °C for 3 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave *N*-(4-bromo-2-chlorophenyl)acetamide (**250r**) (0.12 g, 98%),) as a white solid. Mp 148–150 °C (lit.[221] 151–152 °C); δ_H (500 MHz, $CDCl_3$) 2.23 (3H, s, CH_3), 7.38 (1H, dd, *J* 8.9, 2.2 Hz, 5-H), 7.51 (1H, d, *J* 2.2 Hz, 3-H), 7.57 (1H, s, NH), 8.28 (1H, d, *J* 8.9 Hz, 6-H); δ_C (126 MHz, $CDCl_3$) 24.9 (CH_3), 116.2 (C), 122.6 (CH), 123.2 (C), 130.8 (CH), 131.4 (CH), 133.8 (C), 168.2 (C); *m/z* (ESI) 272 (MNa^+. 100%).

***N*-(2-Acetyl-4-bromophenyl)acetamide (250s)**[222]



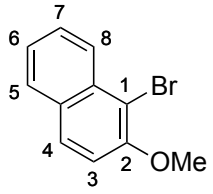
N-(2-Acetyl-4-bromophenyl)acetamide (**250s**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using *N*-(2-acetylphenyl)acetamide (90 mg, 0.50 mmol) in a co-solvent system of [BMIM]NTf_2 (0.3 mL) and toluene (0.1 mL) and performing the reaction at 40 °C for 3.5 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave *N*-(2-acetyl-4-bromophenyl)acetamide (**250s**) (0.13 g, 99%),) as a white solid. Mp 158–160 °C. Spectroscopic data was consistent with the literature.[222] δ_H (500 MHz, $CDCl_3$) 2.21 (3H, s, CH_3), 2.64 (3H, s, CH_3), 7.61 (1H, dd, *J* 9.1, 2.3 Hz, 5-H), 7.96 (1H, d, *J* 2.3 Hz, 3-H), 8.66 (1H, d, *J* 9.1 Hz, 6-H), 11.56 (1H, s, NH); δ_C (126 MHz, $CDCl_3$) 25.5 (CH_3), 28.6 (CH_3), 114.4 (C), 122.3 (CH), 123.0 (C), 134.0 (CH), 137.6 (CH), 139.9 (C), 169.4 (C), 201.6 (C); *m/z* (ESI) 278 (MNa^+. 97%).

1-Bromo-4-methoxynaphthalene (250t)[223]



1-Bromo-4-methoxynaphthalene (**250t**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 1-methoxynaphthalene (80 mg, 0.50 mmol) and performing the reaction at 40 °C for 2 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-bromo-4-methoxynaphthalene (**250t**) (0.11 g, 89%) as a colourless oil. Spectroscopic data was consistent with the literature.[223] δ_H (500 MHz, $CDCl_3$) 3.98 (3H, s, OCH_3), 6.66 (1H, d, *J* 8.3 Hz, 3-H), 7.55 (1H, ddd, *J* 8.3, 6.9, 1.1 Hz, 7-H), 7.63 (1H, ddd, *J* 8.4, 6.9, 1.2 Hz, 6-H), 7.67 (1H, d, *J* 8.3 Hz, 2-H), 8.21 (1H, br d, *J* 8.4 Hz, 5-H), 8.31 (1H, br d, *J* 8.3 Hz, 8-H); δ_C (126 MHz, $CDCl_3$) 55.7 (CH_3), 104.5 (CH), 113.3 (C), 122.5 (CH), 126.0 (CH), 126.8 (C), 126.9 (CH), 127.8 (CH), 129.5 (CH), 132.5 (C), 155.3 (C); *m/z* (EI) 236 (M^+. 100%), 221 (42), 193 (54), 114 (44), 84 (35), 63 (11).

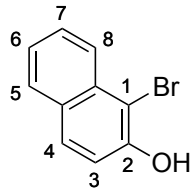
1-Bromo-2-methoxynaphthalene (250u)[224]



1-Bromo-2-methoxynaphthalene (**250u**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 2-methoxynaphthalene (80 mg, 0.50 mmol) and performing the reaction at 40 °C for 2 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-bromo-2-methoxynaphthalene (**250u**) (0.11 g, 93%) as a white solid. Mp 80–82 °C (lit.[224] 82 °C); δ_H (500 MHz, $CDCl_3$) 4.03 (3H, s, OCH_3), 7.27 (1H, d, *J* 8.9 Hz, 3-H), 7.40 (1H, ddd, *J* 8.1, 6.8, 1.0 Hz, 6-H), 7.57 (1H, ddd, *J* 8.4, 6.8, 1.2 Hz, 7-H), 7.79 (1H, d, *J* 8.1 Hz, 5-H), 7.82 (1H, d, *J* 8.9 Hz, 4-H), 8.24 (1H, d, *J* 8.4 Hz, 8-H); δ_C (126 MHz, $CDCl_3$) 57.1 (CH_3), 108.7 (C), 113.6 (CH), 124.3 (CH), 126.1 (CH), 127.8 (CH), 128.1 (CH), 129.0 (CH), 129.8 (C), 133.2 (C), 153.8 (C); *m/z* (EI) 238 (M^+.

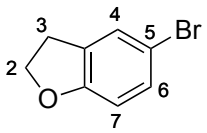
100%), 195 (70), 175 (32), 149 (29), 127 (27), 114 (39), 84 (91), 69 (33), 55 (60).

1-Bromo-2-naphthol (250v)[225]



1-Bromo-2-naphthol (**250v**) was synthesised as described for 3-bromo-4-methoxybenzoic acid (**250e**) using 2-naphthol (70 mg, 0.50 mmol) and performing the reaction at 40 °C for 1 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-bromo-2-naphthol (**250v**) (0.10 g, 90%) as a pale green solid. Mp 72–74 °C (lit.[225] 76–78 °C); δ_H (500 MHz, $CDCl_3$) 5.95 (1H, s, OH), 7.28 (1H, d, *J* 8.8 Hz, 3-H), 7.40 (1H, ddd, *J* 8.0, 6.9, 1.2 Hz, 6-H), 7.58 (1H, ddd, *J* 8.5, 6.9, 1.2 Hz, 7-H), 7.74 (1H, d, *J* 8.8 Hz, 4-H), 7.79 (1H, br d, *J* 8.0 Hz, 5-H), 8.04 (1H, br d, *J* 8.5 Hz, 8-H); δ_C (126 MHz, $CDCl_3$) 106.2 (C), 117.2 (CH), 124.2 (CH), 125.4 (CH), 127.9 (CH), 128.2 (CH), 129.4 (CH), 129.7 (C), 132.3 (C), 150.6 (C); *m/z* (EI) 222 (M^+. 100%), 144 (12), 114 (38).

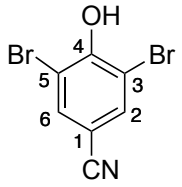
5-Bromo-2,3-dihydrobenzofuran (250w)



5-Bromo-2,3-dihydrobenzofuran (**250w**) was synthesised as described for 4-bromoanisole (**250a**) (Method A) using 2,3-dihydrobenzofuran (56 µL, 0.50 mmol) and performing the reaction at 40 °C for 1 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 5-bromo-2,3-dihydrobenzofuran (**250w**) (97 mg, 98%) as a white solid. Mp 48–50 °C; ν_{max}/cm^{-1} (neat) 2903 (CH), 1478, 1464, 1231, 1155, 1105, 978, 932, 812; δ_H (500 MHz, $CDCl_3$) 3.20 (2H, t, *J* 8.7 Hz, 3-H_2), 4.57 (2H, t, *J* 8.7 Hz, 2-H_2), 6.66 (1H, d, *J* 8.4 Hz, 7-H), 7.19 (1H, dd, *J* 8.4, 1.6 Hz, 6-H), 7.28 (1H, br s, 4-H); δ_C (126 MHz, $CDCl_3$) 29.8 (CH_2), 71.7 (CH_2), 110.9 (CH), 112.1 (C), 128.0 (CH), 129.6 (C),

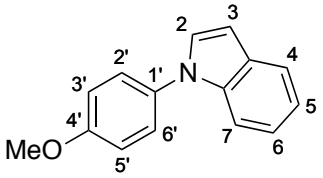
130.8 (CH), 159.4 (C); *m/z* (EI) 197.9680 (M^+, $C_8H_7{}^{79}BrO$ requires 197.9680), 118 (20%), 91 (81), 63 (28).

3,5-Dibromo-4-hydroxybenzonitrile (250x)



3,5-Dibromo-4-hydroxybenzonitrile (**250x**) was synthesised as described for 3-bromo-4-methoxybenzoic acid (**250e**) using 4-cyanophenol (60.0 mg, 0.500 mmol) and *N*-bromosuccinimide (190 mg, 1.05 mmol) and performing the reaction at 40 °C for 2.5 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 3,5-dibromo-4-hydroxybenzonitrile (**250x**) (126 mg, 91%) as a white solid. Mp 190−192; ν_{max}/cm^{-1} (neat) 3406 (OH), 2926 (CH), 2230, (CN), 1464, 1325, 1200, 1134, 1055, 893, 800, 745; δ_H (500 MHz, $CDCl_3$) 6.40 (1H, s, OH), 7.77 (2H, s, 2-H and 6-H); δ_C (126 MHz, $CDCl_3$) 106.6 (C), 110.4 (2 × C), 116.2 (C), 135.7 (2 × CH), 153.6 (C); *m/z* (ESI) 275.8499 ([M–H]$^-$. $C_7H_2Br^{79}Br^{81}BrNO$ requires 275.8488).

1-(4'-Methoxyphenyl)-1*H*-indole (252a)[226]

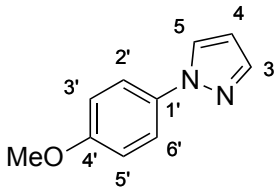


Method A- Iron(III) trichloride (4.00 mg, 0.0250 mmol) was dissolved in [BMIM]NTf_2 (22.0 µL, 0.0750 mmol), pre-stirred for 0.5 h at room temperature and then added to a solution of *N*-bromosuccinimide (178 mg, 1.00 mmol) in toluene (1.0 mL). Anisole (108 µL, 1.00 mmol) was then added and the mixture was stirred at 40 °C for 4 h. The reaction mixture was then cooled to room temperature and the indole (176 mg, 1.50 mmol), copper(I) iodide (19.0 mg, 0.100 mmol), *N*,*N*′-dimethylethylenediamine (22.0 µL, 0.200 mmol), cesium carbonate (652 mg, 2.00 mmol) and water (0.70 mL) were added. The reaction mixture was degassed

under argon for 0.1 h before heated to 130 °C for 18 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL), washed with a 1 M sodium thiosulfate solution (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (175 mg, 78%) as a white solid. Mp 56–58 °C (lit.[226] 57–59 °C); δ_H (500 MHz, $CDCl_3$) 3.95 (3H, s, OCH_3), 6.79 (1H, dd, *J* 3.2, 0.8 Hz, 3-H), 7.09–7.14 (2H, m, 3'-H and 5'-H), 7.27–7.36 (2H, m, 5-H and 6-H), 7.39 (1H, d, *J* 3.2 Hz, 2-H), 7.47–7.52 (2H, m, 2'-H and 6'-H), 7.59 (1H, dd, *J* 8.0, 0.8 Hz, 4-H), 7.82 (1H, br d, *J* 8.0 Hz, 7-H); δ_C (126 MHz, $CDCl_3$) 55.7 (CH_3), 103.1 (CH), 110.5 (CH), 114.9 (2 × CH), 120.2 (CH), 121.2 (CH), 122.3 (CH), 126.1 (2 × CH), 128.4 (CH), 129.1 (C), 132.9 (C), 136.4 (C), 158.3 (C); *m/z* (ESI) 224 (MH^+. 100%).

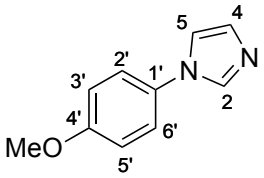
Method B- Iron(III) trichloride (2.00 mg, 0.0125 mmol) was dissolved in [BMIM]NTf_2 (11.0 µL, 0.0375 mmol), pre-stirred for 0.5 h at room temperature and then added to a solution of *N*-iodosuccinimide (113 mg, 0.500 mmol) in toluene (0.50 mL). Anisole (54.0 µL, 0.500 mmol) was then added and the mixture was stirred at 40 °C for 3 h. The reaction mixture was then cooled to room temperature and the indole (88.0 mg, 0.750 mmol), copper(I) iodide (10.0 mg, 0.0500 mmol), *N*,*N*′-dimethylethylenediamine (11.0 µL, 0.100 mmol), cesium carbonate (313 mg, 1.00 mmol) and water (0.30 mL) were added. The reaction mixture was degassed under argon for 0.1 h before heated to 130 °C for 20 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL), washed with a 1 M sodium thiosulfate solution (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (0.099 g, 89%) as a white solid. Spectroscopic data as described above.

1-(4'-Methoxyphenyl)-1*H*-pyrazole (252b)[227]



1-(4'-Methoxyphenyl)-1*H*-pyrazole (**252b**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using anisole (1.08 mL, 10.0 mmol) and pyrazole (1.02 g, 15.0 mmol). The bromination step was carried out at 40 °C for 4 h and the *N*-arylation step at 150 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-(4'-methoxyphenyl)-1*H*-pyrazole (**252b**) (1.65 g, 95%) as a light brown oil. Spectroscopic data was consistent with the literature.[227] δ_H (400 MHz, $CDCl_3$) 3.84 (3H, s, OCH_3), 6.44 (1H, dd, *J* 2.0, 1.5 Hz, 4-H), 6.94–7.00 (2H, m, 3'-H and 5'-H), 7.56–7.62 (2H, m, 2'-H and 6'-H), 7.69 (1H, d, *J* 2.0 Hz, ArH) 7.82 (1H, d, *J* 2.0 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 107.2 (CH), 114.5 (2 × CH), 120.8 (2 × CH), 126.8 (CH), 134.0 (C), 140.6 (CH), 158.2 (C); *m/z* (ESI) 197 (MNa^+. 100%).

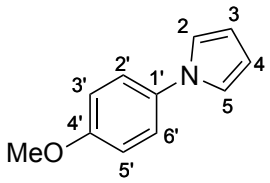
1-(4'-Methoxyphenyl)-1*H*-imidazole (252c)[228]



1-(4'-Methoxyphenyl)-1*H*-imidazole (**252c**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using anisole (108 µL, 1.00 mmol) and imidazole (102 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 4 h and the *N*-arylation step at 150 °C for 24 h. Purification by flash column chromatography (dichloromethane/methanol 19:1) gave 1-(4'-methoxyphenyl)-1*H*-imidazole (**252c**) (132 mg, 76%) as an off-white solid. Mp 60–62 °C (lit.[228] 61–63 °C); δ_H (500 MHz, $CDCl_3$) 3.79 (3H, s, OCH_3), 6.90–6.95 (2H, m, 3'-H and 5'-H), 7.10–7.20 (2H, br m, 4-H and 5-H), 7.21–7.27 (2H, m, 2'-H and 6'-H), 7.72 (1H, br s, 2-H); δ_C (126 MHz, $CDCl_3$) 55.6 (CH_3), 114.9 (2 × CH), 118.8 (CH), 123.1 (2 ×

CH), 130.1 (CH), 130.7 (C), 135.8 (CH), 158.9 (C); *m/z* (ESI) 175 (MH^+. 100%), 160 (28), 132 (6).

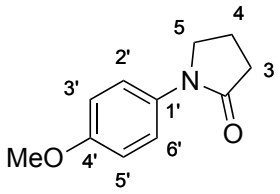
1-(4'-Methoxyphenyl)-1*H*-pyrrole (252d)[229]



Method A- 1-(4'-Methoxyphenyl)-1*H*-pyrrole (**252d**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using anisole (108 µL, 1.00 mmol) and pyrrole (104 µL, 1.50 mmol). The bromination step was carried out at 40 °C for 4 h and the *N*-arylation step at 150 °C for 36 h. Purification by flash column chromatography (petroleum ether) gave 1-(4'-methoxyphenyl)-1*H*-pyrrole (**252d**) (88.0 mg, 51%) as a white solid. Mp 98–100 °C (lit.[229] 104–108 °C); δ_H (500 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 6.35 (2H, t, *J* 2.2 Hz, 3-H and 4-H), 6.94–6.99 (2H, m, 3'-H and 5'-H), 7.02 (2H, t, *J* 2.2 Hz, 2-H and 5-H), 7.31–7.35 (2H, m, 2'-H and 6'-H); δ_C (126 MHz, $CDCl_3$) 55.6 (CH_3), 109.9 (2 × CH), 114.6 (2 × CH), 119.7 (2 × CH), 122.2 (2 × CH), 134.5 (C), 157.7 (C); *m/z* (ESI) 196 (MNa^+. 100%).

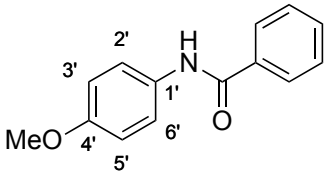
Method B- 1-(4'-Methoxyphenyl)-1*H*-pyrrole (**252d**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method B) using anisole (54 µL, 0.50 mmol) and pyrrole (49 µL, 0.75 mmol). The iodination step was carried out at 40 °C for 3 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-(4'-methoxyphenyl)-1*H*-pyrrole (**252d**) (59 mg, 68%) as a white solid. Spectroscopic data as described above.

1-(4'-Methoxyphenyl)pyrrolidin-2-one (252e)[230]



1-(4'-Methoxyphenyl)pyrrolidin-2-one (**252e**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using anisole (108 μL, 1.00 mmol) and pyrrolidin-2-one (128 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 4 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (dichloromethane/methanol 49:1) gave 1-(4'-methoxyphenyl)pyrrolidin-2-one (**252e**) (111 mg, 58%) as an off-white solid. Mp 112–114 °C (lit.[230] 113–114 °C); δ_H (500 MHz, $CDCl_3$) 2.14 (2H, quin, *J* 7.9 Hz, 4-H_2), 2.58 (2H, t, *J* 7.9 Hz, 3-H_2), 3.79 (3H, s, OMe), 3.81 (2H, t, *J* 7.9 Hz, 5-H_2), 6.86–6.92 (2H, m, 3'-H and 5'-H), 7.46–7.51 (2H, m, 2'-H and 6'-H); δ_C (126 MHz, $CDCl_3$) 18.0 (CH_2), 32.5 (CH_2), 49.2 (CH_2), 55.5 (CH_3), 114.0 (2 × CH), 121.8 (2 × CH), 132.6 (C), 156.6 (C), 173.9 (C); *m/z* (ESI) 214 (MNa^+. 100%).

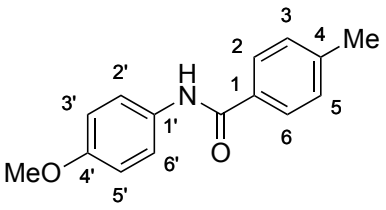
***N*-(4'-Methoxyphenyl)benzamide (252f)[231]**



N-(4'-Methoxyphenyl)benzamide (**252f**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using anisole (108 μL, 1.00 mmol) and benzamide (182 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave *N*-(4'-methoxyphenyl)benzamide (**252f**) (177 mg, 78%) as a white solid. Mp 152–154 °C (lit.[231] 153–155 °C); δ_H (500 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 6.87–6.93 (2H, m, 3'-H and 5'-H), 7.44–7.56 (5H, m, 2'-H, 6'-H and 3 × ArH), 7.80 (1H, br s, NH), 7.83–7.88 (2H, m, 2 × ArH); δ_C (126 MHz, $CDCl_3$) 55.5 (CH_3), 114.3 (2 × CH), 122.1 (2 × CH), 127.0 (2 × CH), 128.7 (2 × CH), 131.0 (C), 131.7 (CH), 135.1 (C),

156.7 (C), 165.6 (C); *m/z* (ESI) 250 (MNa^+. 100%).

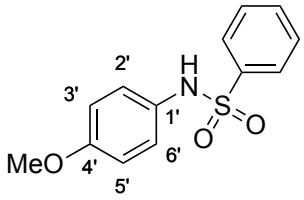
N-(4'-Methoxyphenyl)-4-methylbenzamide (252g)[231]



Method A- *N*-(4'-Methoxyphenyl)-4-methylbenzamide (**252g**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using anisole (108 µL, 1.00 mmol) and *p*-toluamide (203 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave *N*-(4'-methoxyphenyl)-4-methylbenzamide (**252g**) (213 mg, 88%) as a light brown solid. Mp 156–158 °C (lit.[231] 157–159 °C); δ_H (500 MHz, $CDCl_3$) 2.40 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 6.85–6.90 (2H, m, 3'-H and 5'-H), 7.24 (2H, d, *J* 8.0 Hz, 3-H and 5-H), 7.50–7.55 (2H, m, 2'-H and 6'-H), 7.75 (2H, d, *J* 8.0 Hz, 2-H and 6-H), 7.88 (1H, s, NH); δ_C (126 MHz, $CDCl_3$) 21.5 (CH_3), 55.5 (CH_3), 114.2 (2 × CH), 122.2 (2 × CH), 127.0 (2 × CH), 129.4 (2 × CH), 131.2 (C), 132.2 (C), 142.1 (C), 156.5 (C), 165.7 (C); *m/z* (ESI) 264 (MNa^+. 100%).

Method B- *N*-(4'-Methoxyphenyl)-4-methylbenzamide (**252g**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method B) using anisole (54.0 µL, 0.500 mmol) and *p*-toluamide (102 mg, 0.750 mmol). The iodination step was carried out at 40 °C for 3 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave *N*-(4'-methoxyphenyl)-4-methylbenzamide (**252g**) (119 mg, 99%) as a light brown solid. Spectroscopic data as described above.

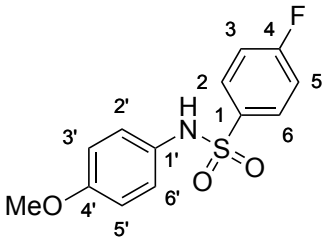
***N*-(4'-Methoxyphenyl)benzenesulfonamide (252h)[232]**



Method A- *N*-(4'-Methoxyphenyl)benzenesulfonamide (**252h**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using anisole (108 μL, 1.00 mmol) and benzenesulfonamide (236 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave *N*-(4'-methoxyphenyl)benzenesulfonamide (**252h**) (231 mg, 88%) as a brown solid. Mp 90–92 °C. Spectroscopic data was consistent with the literature.[232] δ_H (400 MHz, $CDCl_3$) 3.75 (3H, s, OCH_3), 6.71–6.78 (3H, m, 3'-H, 5'-H and NH), 6.95–7.01 (2H, m, 2'-H and 6'-H), 7.39–7.45 (2H, m, 2 × ArH), 7.53 (1H, tt, *J* 7.6, 1.2 Hz, ArH), 7.70–7.74 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 55.4 (CH_3), 114.5 (2 × CH), 125.3 (2 × CH), 127.3 (2 × CH), 129.0 (2 × CH and C), 132.9 (CH), 138.9 (C), 157.9 (C); *m/z* (ESI) 286 (MNa^+. 100%).

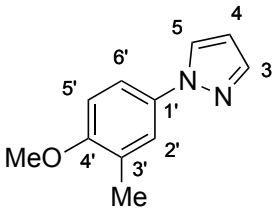
Method B- *N*-(4'-Methoxyphenyl)benzenesulfonamide (**252h**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method B) using anisole (54.0 μL, 0.500 mmol) and benzenesulfonamide (118 mg, 0.750 mmol). The iodination step was carried out at 40 °C for 3 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave *N*-(4'-methoxyphenyl)benzenesulfonamide (**252h**) (125 mg, 95%) as a brown solid. Spectroscopic data as described above.

4-Fluoro-*N*-(4'-methoxyphenyl)benzenesulfonamide (252i)



4-Fluoro-*N*-(4'-methoxyphenyl)benzenesulfonamide (**252i**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using anisole (108 μL, 1.00 mmol) and 4-fluorobenzenesulfonamide (263 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave 4-fluoro-*N*-(4'-methoxyphenyl)benzenesulfonamide (**252i**) (231 mg, 82%) as a light brown solid. Mp 102–104 °C; ν_{max}/cm^{-1} (neat) 3262 (NH), 2937 (CH), 1592 (C=C), 1508, 1495, 1247, 1241, 1165, 1153, 1090, 837, 754; δ_H (500 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 6.74–6.79 (3H, m, 3'-H, 5'-H and NH), 6.95–7.00 (2H, m, 2'-H and 6'-H), 7.06–7.12 (2H, m, 3-H and 5-H), 7.69–7.74 (2H, m, 2-H and 6-H); δ_C (126 MHz, $CDCl_3$) 55.4 (CH_3), 114.5 (2 × CH), 116.2 (2 × CH, d, $^2J_{CF}$ 22.6 Hz), 125.7 (2 × CH), 128.5 (C), 130.1 (2 × CH, d, $^3J_{CF}$ 9.4 Hz), 134.9 (C, d, $^4J_{CF}$ 3.2 Hz), 158.2 (C), 165.2 (C, d, $^1J_{CF}$ 255.1 Hz); *m/z* (ESI) 304.0405 (MNa^+. $C_{13}H_{12}FNNaO_3S$ requires 304.0414).

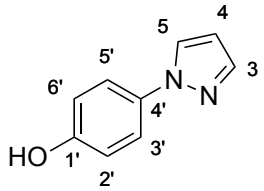
1-(4'-Methoxy-3'-methylphenyl)-1*H*-pyrazole (253a)



1-(4'-Methoxy-3'-methylphenyl)-1*H*-pyrazole (**253a**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using 2-methylanisole (124 μL, 1.00 mmol) and pyrazole (102 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 4 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-(4'-

methoxy-3'-methylphenyl)-1*H*-pyrazole (**253a**) (152 mg, 81%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2928 (CH), 1519 (C=C), 1504, 1239, 1046, 909, 730; δ_H (500 MHz, $CDCl_3$) 2.28 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 6.42 (1H, t, *J* 2.0 Hz, 4-H), 6.86 (1H, d, *J* 8.7 Hz, 5'-H), 7.42 (1H, dd, *J* 8.7, 2.6 Hz, 6'-H), 7.48 (1H, d, *J* 2.6 Hz, 2'-H), 7.68 (1H, d, *J* 2.0 Hz, ArH), 7.81 (1H, d, *J* 2.0 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 16.4 (CH_3), 55.6 (CH_3), 107.0 (CH), 110.2 (CH), 117.8 (CH), 122.3 (CH), 126.8 (CH), 127.8 (C), 133.5 (C), 140.5 (CH), 156.4 (C); *m/z* (ESI) 211.0838 (MNa^+. $C_{11}H_{12}N_2NaO$ requires 211.0842).

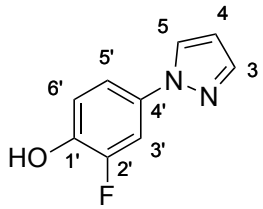
4'-(1*H*-Pyrazol-1-yl)phenol (253b)[233]



Method A- 4'-(1*H*-Pyrazol-1-yl)phenol (**253b**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using phenol (94.0 mg, 1.00 mmol) and pyrazole (102 mg, 1.50 mmol). The bromination step was carried out at room temperature for 1 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (dichloromethane/methanol 49:1) gave 4'-(1*H*-pyrazol-1-yl)phenol (**253b**) (106 mg, 66%) as a light brown oil. Spectroscopic data was consistent with the literature.[233] δ_H (500 MHz, $CDCl_3$) 6.45 (1H, t, *J* 2.0 Hz, 4-H), 6.80–6.84 (2H, m, 2'-H and 6'-H), 7.40–7.44 (2H, m, 3'-H and 5'-H), 7.72 (1H, d, *J* 2.0 Hz, ArH), 7.78 (1H, d, *J* 2.0 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 107.2 (CH), 116.3 (2 × CH), 122.0 (2 × CH), 128.1 (CH), 132.8 (C), 140.4 (CH), 156.1 (C); *m/z* (ESI) 159 ($[M–H]^-$. 100%).

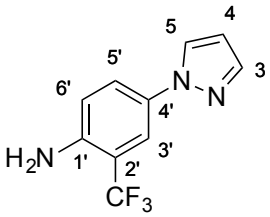
Method B- 4'-(1*H*-Pyrazol-1-yl)phenol (**253b**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method B) using phenol (47 mg, 0.50 mmol) and pyrazole (51 mg, 0.75 mmol). The iodination step was carried out at 40 °C for 0.5 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (dichloromethane/methanol 49:1) gave 4'-(1*H*-pyrazol-1-yl)phenol (**253b**) (57 mg, 71%) as a light brown oil. Spectroscopic data as described above.

2'-Fluoro-4'-(1*H*-pyrazol-1-yl)phenol (253c)



2'-Fluoro-4'-(1*H*-pyrazol-1-yl)phenol (**253c**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using 2-fluorophenol (89.0 µL, 1.00 mmol) and pyrazole (102 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 3 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 2'-fluoro-4'-(1*H*-pyrazol-1-yl)phenol (**253c**) (104 mg, 64%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3123 (OH), 2970 (CH), 1526, 1516, 1401, 1288, 1248, 1186, 1039, 753; δ_H (500 MHz, $CDCl_3$) 6.45 (1H, t, *J* 2.0 Hz, 4-H), 6.49 (1H, s, OH), 7.02 (1H, t, *J* 8.9 Hz, 6'-H), 7.28 (1H, ddd, *J* 8.9, 2.5, 1.4 Hz, 5'-H), 7.44 (1H, dd, *J* 11.4, 2.5 Hz, 3'-H), 7.71 (1H, d, *J* 2.0 Hz, ArH), 7.80 (1H, d, *J* 2.0 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 107.6 (CH), 108.9 (CH, d, $^2J_{CF}$ 22.6 Hz), 116.2 (CH, d, $^3J_{CF}$ 3.3 Hz), 118.1 (CH, d, $^4J_{CF}$ 3.1 Hz), 127.7 (CH), 133.0 (C, d, $^3J_{CF}$ 8.6 Hz), 140.9 (CH), 143.2 (C, d, $^2J_{CF}$ 13.7 Hz), 151.3 (C, d, $^1J_{CF}$ 241.2 Hz); *m/z* (ESI) 177.0465 ([M–H]$^-$. $C_9H_6FN_2O$ requires 177.0470).

4'-(1*H*-Pyrazol-1-yl)-2'-(trifluoromethyl)aniline (253d)

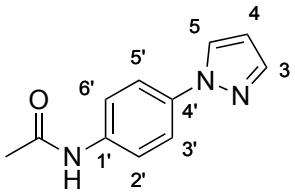


Method A- 4'-(1*H*-Pyrazol-1-yl)-2'-(trifluoromethyl)aniline (**253d**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using 2-trifluoromethylaniline (126 µL, 1.00 mmol) and pyrazole (102 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 7 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 4'-(1*H*-pyrazol-1-yl)-2'-(trifluoromethyl)aniline (**253d**) (148 mg,

65%) as a brown oil. ν_{max}/cm^{-1} (neat) 3365 (NH), 2935 (CH), 1641, 1521, 1506, 1299, 1142, 1106, 1037, 749; δ_H (500 MHz, $CDCl_3$) 4.24 (2H, s, NH_2), 6.44 (1H, t, *J* 2.0 Hz, 4-H), 6.81 (1H, d, *J* 8.7 Hz, 6'-H), 7.61 (1H, dd, *J* 8.7, 2.4 Hz, 5'-H), 7.69 (1H, d, *J* 2.0 Hz, ArH), 7.74 (1H, d, *J* 2.4 Hz, 3'-H), 7.80 (1H, d, *J* 2.0 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 107.4 (CH), 113.9 (C, q, $^2J_{CF}$ 30.7 Hz), 118.0 (CH), 118.2 (CH, q, $^3J_{CF}$ 5.5 Hz), 124.4 (C, q, $^1J_{CF}$ 272.5 Hz), 124.5 (CH), 126.8 (CH), 131.4 (C), 140.7 (CH), 143.2 (C); *m/z* (ESI) 250.0556 (MNa^+. $C_{10}H_8F_3N_3Na$ requires 250.0563).

Method B- 4'-(1*H*-Pyrazol-1-yl)-2'-(trifluoromethyl)aniline (**253d**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method B) using 2-trifluoromethylaniline (63 μL, 0.50 mmol) and pyrazole (51 mg, 0.75 mmol). The iodination step was carried out at 40 °C for 6 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 4'-(1*H*-pyrazol-1-yl)-2'-(trifluoromethyl)aniline (**253d**) (90 mg, 79%) as a brown oil. Spectroscopic data as described above.

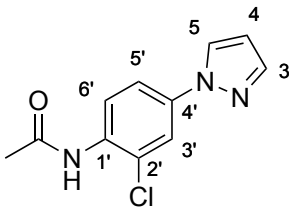
N-[4'-(1*H*-Pyrazol-1-yl)phenyl]acetamide (243e)



N-[4'-(1*H*-Pyrazol-1-yl)phenyl]acetamide (**253e**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using acetanilide (136 mg, 1.00 mmol) and pyrazole (102 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 6 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-[4'-(1*H*-pyrazol-1-yl)phenyl]acetamide (**253e**) (152 mg, 76%) as a brown solid. Mp 134–136 °C; ν_{max}/cm^{-1} (neat) 3304 (NH), 3062 (CH), 1667 (CO), 1614, 1555, 1525, 1398, 1330, 1054, 1036, 940, 826; δ_H (500 MHz, $CDCl_3$) 2.16 (3H, s, CH_3), 6.45 (1H, t, *J* 2.1 Hz, 4-H), 7.55–7.61 (4H, m, 2'-H, 3'-H, 5'-H and 6'-H), 7.70 (1H, d, *J* 2.1 Hz, ArH), 7.80 (1H, br s, NH), 7.86 (1H, d, *J* 2.1 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 24.4 (CH_3), 107.6 (CH), 119.9 (2 × CH), 120.9 (2 × CH), 127.0 (CH), 136.4

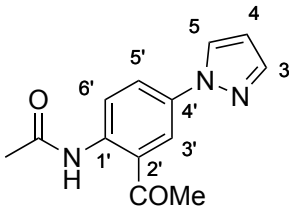
(C), 136.6 (C), 141.0 (CH), 169.0 (C); *m/z* (ESI) 224.0791 (MNa^+. $C_{11}H_{11}N_3NaO$ requires 224.0794).

N-[2'-Chloro-4'-(1*H*-pyrazol-1'-yl)phenyl]acetamide (253f)



N-[2'-Chloro-4'-(1*H*-pyrazol-1'-yl)phenyl]acetamide (**253f**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using *N*-(2-chlorophenyl)acetamide (170 mg, 1.00 mmol) and pyrazole (102 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 8 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave *N*-[2'-chloro-4'-(1*H*-pyrazol-1'-yl)phenyl]acetamide (**253f**) (149 mg, 63%) as a brown solid. Mp 120–122 °C; ν_{max}/cm^{-1} (neat) 3264 (NH), 3011 (CH), 1671 (CO), 1522, 1396, 1302, 1053, 944, 757; δ_H (500 MHz, $CDCl_3$) 2.26 (3H, s, CH_3), 6.47 (1H, t, *J* 2.1 Hz, 4-H), 7.53 (1H, dd, *J* 9.0, 2.5 Hz, 5'-H), 7.62 (1H, br s, NH), 7.71 (1H, d, *J* 2.1 Hz, ArH), 7.83 (1H, d, *J* 2.5 Hz, 3'-H), 7.87 (1H, d, *J* 2.1 Hz, ArH), 8.47 (1H, d, *J* 9.0 Hz, 6'-H); δ_C (126 MHz, $CDCl_3$) 24.8 (CH_3), 108.0 (CH), 117.8 (CH), 119.9 (CH), 122.3 (CH), 123.6 (C), 126.7 (CH), 132.9 (C), 136.4 (C), 141.4 (CH), 168.4 (C); *m/z* (ESI) 258.0401 (MNa^+. $C_{11}H_{10}N_3NaO^{35}Cl$ requires 258.0405).

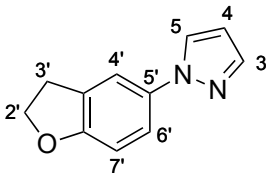
N-[2'-Acetyl-4'-(1*H*-pyrazol-1-yl)phenyl]acetamide (253g)



N-[2'-Acetyl-4'-(1*H*-pyrazol-1-yl)phenyl]acetamide (**253g**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using *N*-(2-acetylphenyl)acetamide (178 mg, 1.00 mmol) and pyrazole (102 mg, 1.50 mmol).

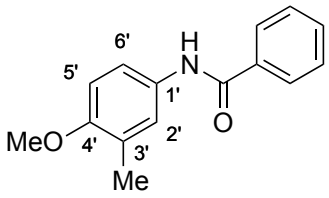
The bromination step was carried out at 40 °C for 7 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave *N*-[2'-acetyl-4'-(1*H*-pyrazol-1-yl)phenyl]acetamide (**253g**) (129 mg, 53%) as a yellow solid. Mp 146–148 °C; ν_{max}/cm^{-1} (neat) 3241 (NH), 3001 (CH), 1693 (CO), 1655 (CO), 1594, 1527, 1509, 1361, 1224, 1041, 946, 755; δ_H (500 MHz, $CDCl_3$) 2.22 (3H, s, CH_3), 2.71 (3H, s, CH_3), 6.47 (1H, t, *J* 2.1 Hz, 4-H), 7.68–7.73 (2H, m, ArH), 7.90 (1H, d, *J* 2.1 Hz, ArH), 8.29 (1H, d, *J* 2.6 Hz, 3'-H), 8.82 (1H, d, *J* 9.1 Hz, 6'-H), 11.59 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 25.5 (CH_3), 28.8 (CH_3), 108.0 (CH), 121.6 (CH), 122.3 (C), 122.3 (CH), 124.8 (CH), 126.7 (CH), 134.6 (C), 139.2 (C), 141.3 (CH), 169.5 (C), 202.4 (C); *m/z* (ESI) 266.0904 (MNa^+. $C_{13}H_{13}N_3NaO_2$ requires 266.0900).

1-(2',3'-Dihydrobenzofuran-5'-yl)-1*H*-pyrazole (253h)



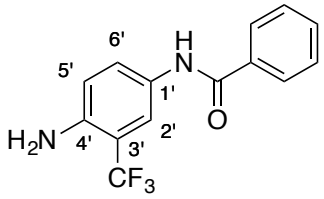
1-(2',3'-Dihydrobenzofuran-5'-yl)-1*H*-pyrazole (**253h**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using 2,3-dihydrobenzofuran (113 μL, 1.00 mmol) and pyrazole (102 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 1.5 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-(2',3'-dihydrobenzofuran-5'-yl)-1*H*-pyrazole (**253h**) (157 mg, 84%) as a brown oil. ν_{max}/cm^{-1} (neat) 2974 (CH), 1516, 1492, 1394, 1228, 1029, 983, 942, 746; δ_H (400 MHz, $CDCl_3$) 3.25 (2H, t, *J* 8.7 Hz, 3'-H_2), 4.62 (2H, t, *J* 8.7 Hz, 2'-H_2), 6.41 (1H, t, *J* 2.1 Hz, 4-H), 6.81 (1H, d, *J* 8.5 Hz, 7'-H), 7.35 (1H, dd, *J* 8.5, 2.4 Hz, 6'-H), 7.51–7.54 (1H, m, 4'-H), 7.67 (1H, d, *J* 2.1 Hz, ArH), 7.78 (1H, d, *J* 2.1 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 29.7 (CH_2), 71.7 (CH_2), 107.0 (CH), 109.3 (CH), 117.2 (CH), 119.7 (CH), 126.9 (CH), 128.3 (C), 134.1 (C), 140.4 (CH), 158.8 (C); *m/z* (ESI) 209.0682 (MNa^+. $C_{11}H_{10}N_2NaO$ requires 209.0685).

***N*-(4'-Methoxy-3'-methylphenyl)benzamide (253i)[234]**



N-(4'-Methoxy-3'-methylphenyl)benzamide (**253i**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using 2-methylanisole (124 µL, 1.00 mmol) and benzamide (182 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave *N*-(4'-methoxy-3'-methylphenyl)benzamide (**253i**) (156 mg, 65%) as a light purple solid. Mp 148–150 °C. Spectroscopic data was consistent with the literature.[234] δ_H (500 MHz, $CDCl_3$) 2.22 (3H, s, CH_3), 3.83 (3H, s, OCH_3), 6.80 (1H, d, *J* 8.7 Hz, 5'-H), 7.36 (1H, d, *J* 1.8 Hz, 2'-H), 7.42–7.49 (3H, m, 6'-H and 2 × ArH), 7.53 (1H, tt, *J* 7.4, 1.2 Hz, ArH), 7.76 (1H, br s, NH), 7.83–7.88 (2H, m, 2 × ArH); δ_C (126 MHz, $CDCl_3$) 16.3 (CH_3), 55.6 (CH_3), 110.2 (CH), 119.2 (CH), 123.5 (CH), 127.0 (2 × CH), 127.3 (C), 128.7 (2 × CH), 130.5 (C), 131.6 (CH), 135.1 (C), 154.9 (C), 165.6 (C); *m/z* (ESI) 264 (MNa^+. 100%).

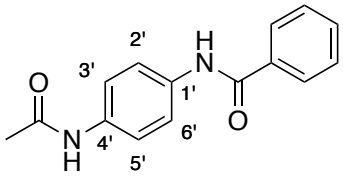
***N*-[4'-Amino-3'-(trifluoromethyl)phenyl]benzamide (253j)**



N-[4'-Amino-3'-(trifluoromethyl)phenyl]benzamide (**253j**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using 2-trifluoromethylaniline (126 µL, 1.00 mmol) and benzamide (133 mg, 1.10 mmol). The bromination step was carried out at 40 °C for 7 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave *N*-[4'-amino-3'-(trifluoromethyl)phenyl]benzamide (253j) (198 mg, 71%) as a light brown solid. Mp 118–120 °C; ν_{max}/cm^{-1} (neat) 3282 (NH), 2927 (CH), 1643 (CO), 1508, 1432, 1310, 1225, 1104, 1051, 694; δ_H (500

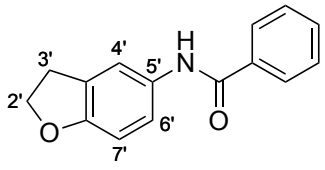
MHz, $CDCl_3$) 4.13 (2H, s, NH_2), 6.77 (1H, d, *J* 8.7 Hz, 5'-H), 7.46−7.51 (2H, m, 2 × ArH), 7.53−7.58 (1H, m, ArH), 7.59−7.67 (2H, m, 2'-H and 6'-H), 7.70 (1H, s, NH), 7.83−7.87 (2H, m, 2 × ArH); δ_C (126 MHz, $CDCl_3$) 113.8 (C, q, $^2J_{CF}$ 30.3 Hz), 117.7 (CH), 119.5 (CH, q, $^3J_{CF}$ 5.1 Hz), 124.5 (C, q, $^1J_{CF}$ 272.2 Hz), 126.4 (CH), 127.0 (2 × CH), 128.4 (C), 128.7 (2 × CH), 131.8 (CH), 134.6 (C), 141.6 (C), 166.0 (C); *m/z* (ESI) 303.0711 (MNa^+. $C_{14}H_{11}F_3N_2NaO$ requires 303.0716).

N-(4'-Acetamidophenyl)benzamide (253k)[235]



N-(4'-Acetamidophenyl)benzamide (**253k**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using 2-trifluoromethylaniline (136 mg, 1.00 mmol) and benzamide (133 mg, 1.10 mmol). The bromination step was carried out at 40 °C for 6 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (dichloromethane/methanol, 98:2) gave *N*-(4'-acetamidophenyl)benzamide (**253k**) (176 mg, 77%) as a brown solid. Mp 146–148 °C. Spectroscopic data was consistent with the literature.[235] δ_H (500 MHz, DMSO-d_6) 2.03 (3H, s, CH_3), 7.49−7.60 (5H, m, 5 × ArH), 7.66−7.71 (2H, m, 2 × ArH), 7.92−7.96 (2H, m, 2 × ArH), 9.91 (1H, s, NH), 10.19 (1H, s, NH); δ_C (126 MHz, DMSO-d_6) 24.4 (CH_3), 119.7 (2 × CH), 121.3 (2 × CH), 128.0 (2 × CH), 128.8 (2 × CH), 131.9 (CH), 134.8 (C), 135.5 (C), 135.7 (C), 165.7 (C), 168.5 (C); *m/z* (EI) 254 (M^+. 100%), 212 (20), 105 (89), 77 (32).

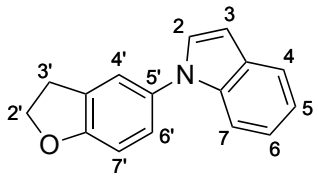
N-(2',3'-Dihydrobenzofuran-5'-yl)benzamide (253l)



N-(2',3'-Dihydrobenzofuran-5'-yl)benzamide (**253l**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using 2,3-dihydrobenzofuran (113 µL, 1.00 mmol) and benzamide (182 mg, 1.50 mmol). The

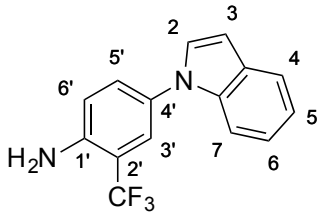
bromination step was carried out at 40 °C for 1.5 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave *N*-(2',3'-dihydrobenzofuran-5'-yl)benzamide (**253l**) (162 mg, 68%) as a brown solid. Mp 156–158 °C; ν_{max}/cm^{-1} (neat) 3268 (NH), 2895 (CH), 1641 (CO), 1529, 1491, 1220, 983, 692; δ_H (500 MHz, $CDCl_3$) 3.21 (2H, t, *J* 8.7 Hz, 3'-H_2), 4.58 (2H, t, *J* 8.7 Hz, 2'-H_2), 6.74 (1H, d, *J* 8.4 Hz, 7'-H), 7.14 (1H, dd, *J* 8.4, 1.5 Hz, 6'-H), 7.42–7.56 (3H, m, 3 × ArH), 7.63 (1H, br s, 4'-H), 7.78–7.88 (3H, m, NH and 2 × ArH); δ_C (126 MHz, $CDCl_3$) 29.9 (CH_2), 71.5 (CH_2), 109.1 (CH), 118.6 (CH), 120.8 (CH), 127.0 (2 × CH), 127.8 (C), 128.7 (2 × CH), 130.8 (C), 131.7 (CH), 135.1 (C), 157.2 (C), 165.7 (C); *m/z* (ESI) 262.0836 (MNa^+. $C_{15}H_{13}NNaO_2$ requires 262.0838).

1-(2',3'-Dihydrobenzofuran-5'-yl)-1H-indole (253m)



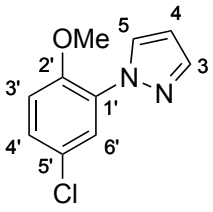
1-(2',3'-Dihydrobenzofuran-5'-yl)-1*H*-indole (**253m**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using 2,3-dihydrobenzofuran (113 μL, 1.00 mmol) and indole (176 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 1.5 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-(2',3'-dihydrobenzofuran-5'-yl)-1*H*-indole (**253m**) (146 mg, 62%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2979 (CH), 1512 (C=C), 1491, 1458, 1213, 1094, 739; δ_H (500 MHz, $CDCl_3$) 3.31 (2H, t, *J* 8.7 Hz, 3'-H_2), 4.68 (2H, t, *J* 8.7 Hz, 2'-H_2), 6.67 (1H, dd, *J* 3.2, 0.6 Hz, 3-H), 6.92 (1H, d, *J* 8.4 Hz, 7'-H), 7.18 (1H, td, *J* 7.8, 1.0 Hz, 6-H), 7.21–7.26 (2H, m, 5-H and 6'-H), 7.29 (1H, d, *J* 3.2 Hz, 2-H), 7.30–7.33 (1H, m, 4'-H), 7.48 (1H, dd, *J* 8.2, 0.6 Hz, 4-H), 7.71 (1H, br d, *J* 7.8 Hz, 7-H); δ_C (126 MHz, $CDCl_3$) 29.9 (CH_2), 71.8 (CH_2), 102.7 (CH), 109.7 (CH), 110.4 (CH), 120.0 (CH), 121.0 (CH), 122.0 (CH), 122.1 (CH), 124.9 (CH), 128.4 (C), 128.5 (CH), 128.9 (C), 132.7 (C), 136.5 (C), 158.9 (C); *m/z* (ESI) 258.0887 (MNa^+. $C_{16}H_{13}NNaO$ requires 258.0889).

4'-(1*H*-Indol-1-yl)-2'-(trifluoromethyl)aniline (253n)



4'-(1*H*-Indol-1-yl)-2'-(trifluoromethyl)aniline (**253n**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using 2-trifluoromethylaniline (126 μL, 1.00 mmol) and indole (176 mg, 1.50 mmol). The bromination step was carried out at 40 °C for 7 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4'-(1*H*-indol-1-yl)-2'-(trifluoromethyl)aniline (**253n**) (146 mg, 53%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3403 (NH), 2923 (CH), 1516, 1459, 1293, 1214, 1105, 772, 741; δ_H (500 MHz, $CDCl_3$) 4.21 (2H, s, NH_2), 6.64 (1H, d, *J* 3.2 Hz, 3-H), 6.77 (1H, d, *J* 8.6 Hz, 6'-H), 7.12−7.24 (3H, m, 2-H, 5-H and 6-H), 7.34−7.39 (2H, m, 4-H and 5'-H), 7.52 (1H, d, *J* 2.4 Hz, 3'-H), 7.67 (1H, d, *J* 7.8 Hz, 7-H); δ_C (126 MHz, $CDCl_3$) 103.3 (CH), 110.2 (CH), 114.3 (C, q, $^2J_{CF}$ 30.6 Hz), 118.1 (CH), 120.3 (CH), 121.2 (CH), 122.4 (CH), 123.3 (CH, q, $^3J_{CF}$ 5.1 Hz), 124.5 (C, q, $^1J_{CF}$ 272.6 Hz), 128.1 (CH), 129.0 (C), 129.7 (CH), 130.1 (C), 136.4 (C), 143.3 (C); *m/z* (ESI) 277.0948 (MH^+. $C_{15}H_{12}F_3N_2$ requires 277.0947).

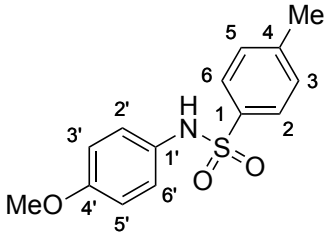
1-(5'-Chloro-2'-methoxyphenyl)-1*H*-pyrazole (253o)



1-(5'-Chloro-2'-methoxyphenyl)-1*H*-pyrazole (**253o**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method A) using 4-chloroanisole (123 μL, 1.00 mmol), iron(III) trichloride (0.0500 mmol), [BMIM]NTf_2 (0.150 mmol) and pyrazole (102 mg, 1.50 mmol). The bromination step was carried out at 70 °C for 5 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 1-(5'-chloro-2'-

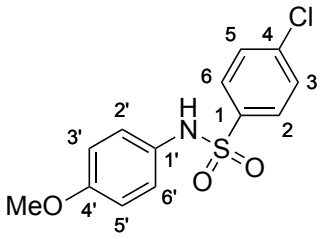
methoxyphenyl)-1*H*-pyrazole (**253o**) (110 mg, 53%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2943 (CH), 1521 (C=C), 1495, 1244, 1024, 750, 704; δ_H (500 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 6.43 (1H, dd, *J* 2.4, 2.0 Hz, 4-H), 6.96 (1H, d, *J* 8.8 Hz, 3'-H), 7.23 (1H, dd, *J* 8.8, 2.6 Hz, 4'-H), 7.70 (1H, d, *J* 2.0 Hz, ArH), 7.81 (1H, d, *J* 2.6 Hz, 6'-H), 8.09 (1H, d, *J* 2.4 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 56.2 (CH_3), 106.7 (CH), 113.4 (CH), 124.7 (CH), 126.1 (C), 127.2 (CH), 130.3 (C), 131.6 (CH), 140.4 (CH), 149.5 (C); *m/z* (ESI) 231.0291 (MNa^+. $C_{10}H_9{}^{35}ClN_2NaO$ requires 231.0296).

N-(4'-Methoxyphenyl)-4-methylbenzenesulfonamide (252j)[236]



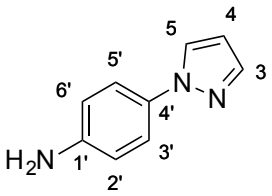
N-(4'-Methoxyphenyl)-4-methylbenzenesulfonamide (**252j**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method B) using anisole (54.0 µL, 0.500 mmol) and *p*-toluenesulfonamide (128 mg, 0.750 mmol). The iodination step was carried out at 40 °C for 3 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave *N*-(4'-methoxyphenyl)-4-methylbenzenesulfonamide (**252j**) (119 mg, 86%) as a light yellow solid. Mp 112–114 °C (lit.[236] 113–114 °C); δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 6.62 (1H, s, NH), 6.72–6.79 (2H, m, 3'-H and 5'-H), 7.72–7.79 (2H, m, 2'-H and 6'-H), 7.21 (2H, d, *J* 8.0 Hz, 3-H and 5-H), 7.59 (2H, d, *J* 8.0 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 55.4 (CH_3), 114.4 (2 × CH), 125.1 (2 × CH), 127.4 (2 × CH), 129.1 (C), 129.6 (2 × CH), 136.0 (C), 143.7 (C), 157.8 (C); *m/z* (EI) 277 (M^+. 35%), 228 (11), 122 (100), 92 (12), 65 (8).

4-Chloro-*N*-(4'-methoxyphenyl)benzenesulfonamide (252k)[237]



4-Chloro-*N*-(4'-methoxyphenyl)benzenesulfonamide (**252k**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method B) using anisole (54.0 μL, 0.500 mmol) and 4-chlorobenzenesulfonamide (144 mg, 0.750 mmol). The iodination step was carried out at 40 °C for 3 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chloro-*N*-(4'-methoxyphenyl)benzenesulfonamide (**252k**) (124 mg, 83%) as a white solid. Mp 138–140 °C (lit.[237] 140–144 °C); δ_H (500 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 6.72–6.81 (3H, m, 3'-H, 5'-H and NH), 6.94–7.02 (2H, m, 2'-H and 6'-H), 7.35–7.42 (2H, m, 3-H and 5-H), 7.60–7.66 (2H, m, 2-H and 6-H); δ_C (126 MHz, $CDCl_3$) 55.4 (CH_3), 114.6 (2 × CH), 125.7 (2 × CH), 128.3 (C), 128.8 (2 × CH), 129.3 (2 × CH), 137.4 (C), 139.4 (C), 158.2 (C); *m/z* (EI) 297 (M^+. 73%), 122 (100), 111 (23), 95 (34), 83 (27), 75 (17), 65 (7), 52 (13).

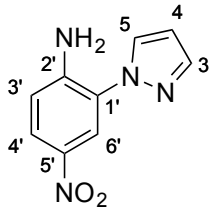
4'-(1*H*-Pyrazol-1-yl)aniline (253q)[238]



4'-(1*H*-Pyrazol-1-yl)aniline (**253q**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method B) using aniline (46.0 μL, 0.500 mmol) and pyrazole (51.0 mg, 0.750 mmol). The iodination step was carried out at 20 °C for 3 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave 4'-(1*H*-pyrazol-1-yl)aniline (**253q**) (73.0 mg, 92%) as a brown oil. Spectroscopic data was consistent with the literature.[238] δ_H (500 MHz, $CDCl_3$) 3.74 (1H, br s, NH_2), 6.41 (1H, t, *J* 2.0 Hz, 4-H), 6.70–6.75 (2H, m, 2'-H and 6'-H), 7.42–7.46 (2H, m, 3'-H

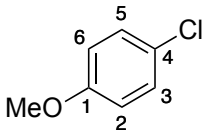
and 5'-H), 7.67 (1H, d, *J* 2.0 Hz, ArH), 7.78 (1H, d, *J* 2.0 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 106.8 (CH), 115.5 (2 × CH), 121.1 (2 × CH), 126.7 (CH), 132.5 (C), 140.2 (CH), 145.2 (C); *m/z* (EI) 159 (M^+. 100%).

4'-Nitro-2'-(1*H*-pyrazol-1-yl)aniline (**253p**)



4'-Nitro-2'-(1*H*-pyrazol-1-yl)aniline (**253p**) was synthesised as described for 1-(4'-methoxyphenyl)-1*H*-indole (**252a**) (Method B) using 4-nitroaniline (69 mg, 0.50 mmol) and pyrazole (51 mg, 0.75 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 4'-nitro-2'-(1*H*-pyrazol-1-yl)aniline (**253p**) (78 mg, 76%) as a yellow solid. Mp 136–138 °C; ν_{max}/cm^{-1} (neat) 3319 (NH), 3080 (CH), 1633, 1614, 1527 (C=C), 1494, 1333, 1316, 707; δ_H (500 MHz, $CDCl_3$) 5.83 (2H, s, NH_2), 6.52 (1H, t, *J* 2.0 Hz, 4-H), 6.80 (1H, d, *J* 9.0 Hz, 3'-H), 7.78 (1H, d, *J* 2.0 Hz, ArH), 7.87 (1H, d, *J* 2.0 Hz, ArH), 8.05 (1H, dd, *J* 9.0, 2.5 Hz, 4'-H), 8.18 (1H, d, *J* 2.5 Hz, 6'-H); δ_C (126 MHz, $CDCl_3$) 107.3 (CH), 115.8 (CH), 119.4 (CH), 124.2 (C), 124.4 (CH), 129.8 (CH), 138.1 (C), 141.2 (CH), 146.7 (C); *m/z* (EI) 204.0654 (M^+, $C_9H_8N_4O_2$ requires 204.0647), 174 (20%), 159 (19), 149 (20), 131 (15), 83 (100), 77 (23), 69 (28). 57 (46).

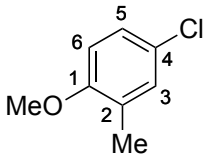
4-Chloroanisole (261a)[239]



Iron(III) chloride (4.00 mg, 0.0250 mmol) was dissolved in $[BMIM]NTf_2$ (22.0 μL, 0.0750 mmol), stirred for 0.5 h at room temperature and then added to a solution of *N*-chlorosuccinimide (140 mg, 1.05 mmol) in tetrahydrofuran (0.60 mL). Anisole (108 μL, 1.00 mmol) was then added and the reaction mixture was stirred at 60 °C

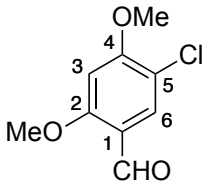
for 18 h, under an atmosphere of air. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M sodium thiosulfate solution (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chloroanisole (**261a**) (131 mg, 92%) as a colourless oil. Spectroscopic data was consistent with the literature.[239] δ_H (500 MHz, $CDCl_3$) 3.77 (3H, s, OCH_3), 6.80–6.85 (2H, m, 2-H and 6-H), 7.21–7.26 (2H, m, 3-H and 5-H); δ_C (126 MHz, $CDCl_3$) 55.5 (CH_3), 115.2 (2 × CH), 125.5 (C), 129.3 (2 × CH), 158.2 (C); *m/z* (EI) 142 (M^+. 100%), 127 (46), 99 (39), 84 (16).

4-Chloro-2-methylanisole (261b)[240]



4-Chloro-2-methylanisole (**261b**) was synthesised as described for 4-chloroanisole (**261a**) using 2-methylanisole (124 µL, 1.00 mmol) and performing the reaction at 60 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave 4-chloro-2-methylanisole (**261b**) (133 mg, 85%) as a yellow oil. Spectroscopic data was consistent with the literature.[240] δ_H (400 MHz, $CDCl_3$) 2.21 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 6.73 (1H, d, *J* 9.2 Hz, 6-H), 7.09–7.15 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 16.2 (CH_3), 55.6 (CH_3), 111.1 (CH), 125.1 (C), 126.4 (CH), 128.6 (C), 130.5 (CH), 156.5 (C); *m/z* (EI) 156 (M^+. 100%), 141 (63), 83 (35), 77 (45), 57 (38).

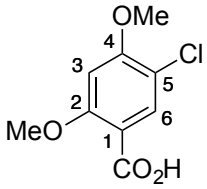
5-Chloro-2,4-dimethoxybenzaldehyde (261c)[241]



5-Chloro-2,4-dimethoxybenzaldehyde (**261c**) was synthesised as described for 4-chloroanisole (**261a**) using 2,4-dimethoxybenzaldehyde (166 mg, 1.00 mmol) and

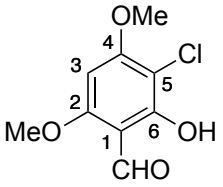
performing the reaction at 60 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 10:1) gave 5-chloro-2,4-dimethoxybenzaldehyde (**261c**) (154 mg, 77%) as a white solid. Mp 130–132 °C. Spectroscopic data was consistent with the literature.[241] δ_H (500 MHz, $CDCl_3$) 3.93 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 6.46 (1H, s, 3-H), 7.81 (1H, s, 6-H), 10.23 (1H, s, CHO); δ_C (126 MHz, $CDCl_3$) 56.0 (CH_3), 56.4 (CH_3), 95.7 (CH), 115.3 (C), 118.7 (C), 129.7 (CH), 160.8 (C), 162.4 (C), 187.2 (CH); *m/z* (ESI) 223 (MNa^+. 100%).

5-Chloro-2,4-dimethoxybenzoic acid (261d)



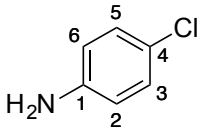
Iron(III) chloride (4.00 mg, 0.0250 mmol) was dissolved in [BMIM]NTf_2 (22.0 µL, 0.0750 mmol), stirred for 0.5 h at room temperature and then added to a solution of *N*-chlorosuccinimide (140 mg, 1.05 mmol) in tetrahydrofuran (0.60 mL). 2,4-Dimethoxybenzoic acid (182 mg, 1.00 mmol) was then added and the reaction mixture was stirred at 60 °C for 24 h, under an atmosphere of air. The reaction mixture was diluted with dichloromethane (20 mL) and extracted with an aqueous solution of 1 M sodium hydroxide (10 mL). The aqueous phase was separated and then acidified with 1 M hydrochloric acid (10 mL), and extracted into dichloromethane (2 × 50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (dichloromethane/methanol, 19:1) gave 5-chloro-2,4-dimethoxybenzoic acid (**261d**) (181 mg, 84%) as a white solid. Mp 166–168 °C. ν_{max}/cm^{-1} (neat) 2970 (CH), 2569 (OH), 1694 (CO), 1599 (C=C), 1243, 1213, 1021, 904, 820, 727; δ_H (500 MHz, $CDCl_3$) 3.98 (3H, s, OCH_3), 4.08 (3H, s, OCH_3), 6.53 (1H, s, 3-H), 8.13 (1H, s, 6-H); δ_C (126 MHz, $CDCl_3$) 56.6 (CH_3), 57.1 (CH_3), 96.0 (CH), 110.6 (C), 116.1 (C), 134.5 (CH), 158.4 (C), 160.0 (C), 164.6 (C); *m/z* (EI) 218.0167 (M^+. $C_9H_9{}^{37}ClO_4$ requires 218.0163), 216 (100%), 199 (47), 169 (42), 142 (22), 78 (27), 63 (32).

5-Chloro-2,4-dimethoxy-6-hydroxybenzaldehyde (261e)



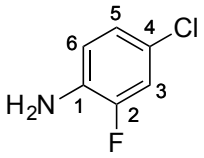
5-Chloro-2,4-dimethoxy-6-hydroxybenzaldehyde (**261e**) was synthesised as described for 5-chloro-2,4-dimethoxybenzoic acid (**261d**) using 2,4-dimethoxy-6-hydroxybenzaldehyde (182 mg, 1.00 mmol) and performing the reaction at 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 5-chloro-2,4-dimethoxy-6-hydroxybenzaldehyde (**261e**) (182 mg, 84%) as a light yellow solid. Mp 184–186 °C; ν_{max}/cm^{-1} (neat) 2953 (CH), 1631 (CO), 1595 (C=C), 1470, 1453, 1417, 1410, 1292, 1227, 1186, 1119, 1100, 790, 731; δ_H (500 MHz, $CDCl_3$) 3.91 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 5.99 (1H, s, 3-H), 10.09 (1H, s, CHO), 12.80 (1H, s, OH); δ_C (126 MHz, $CDCl_3$) 56.0 (CH_3), 56.5 (CH_3), 86.7 (CH), 101.4 (C), 106.1 (C), 160.3 (C), 162.5 (C), 162.8 (C), 192.0 (CH); *m/z* (ESI) 239.0083 (MNa^+. $C_9H_9{}^{35}ClNaO_4$ requires 239.0082).

4-Chloroaniline (261f)[242]



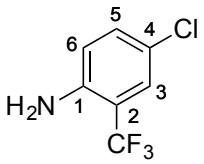
4-Chloroaniline (**261f**) was synthesised as described for 4-chloroanisole (**261a**) using aniline (91 µL, 1.0 mmol) and performing the reaction at 40 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chloroaniline (**261f**) (67 mg, 53%) as a yellow solid. Mp 58–60 °C (lit.[242] 63–65 °C); δ_H (400 MHz, $CDCl_3$) 3.64 (2H, br s, NH_2), 6.56–6.65 (2H, m, 2H and 6-H), 7.07–7.14 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 116.3 (2 × CH), 123.3 (C), 129.2 (2 × CH), 145.1 (C); *m/z* (EI) 127 (M^+. 100%), 92 (16), 84 (19), 64 (19).

4-Chloro-2-fluoroaniline (261g)[243]



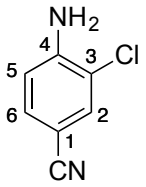
4-Chloro-2-fluoroaniline (**261g**) was synthesised as described for 4-chloroanisole (**261a**) using 2-fluoroaniline (111 mg, 1.00 mmol) and performing the reaction at 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chloro-2-fluoroaniline (**261g**) (109 mg, 75%) as a brown oil. Spectroscopic data was consistent with the literature.[243] δ_H (500 MHz, $CDCl_3$) 3.70 (2H, br s, NH_2), 6.69 (1H, dd, *J* 9.4, 8.5 Hz, 6-H), 6.92 (1H, ddd, *J* 8.5, 2.3, 1.2 Hz, 5-H), 7.00 (1H, dd, *J* 10.8, 2.3 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 115.9 (CH, d, $^2J_{CF}$ 22.0 Hz), 117.3 (CH, d, $^3J_{CF}$ 4.4 Hz), 122.5 (C, d, $^3J_{CF}$ 9.2 Hz), 124.5 (CH, d, $^4J_{CF}$ 3.6 Hz), 133.3 (C, d, $^2J_{CF}$ 13.0 Hz), 151.2 (C, d, $^1J_{CF}$ 242.3 Hz); *m/z* (EI) 145 (M^+. 32%), 84 (100).

4-Chloro-2-trifluoromethylaniline (261h)[244]



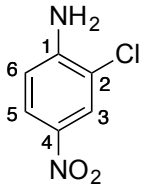
4-Chloro-2-trifluoromethylaniline (**261h**) was synthesised as described for 4-chloroanisole (**261a**) using 2-trifluoromethylaniline (126 µL, 1.00 mmol), iron(III) chloride (8.00 mg, 0.0500 mmol) and [BMIM]NTf2 (44.0 µL, 0.150 mmol) in tetrahydrofuran (0.60 mL). The reaction was performed at 70 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 4-chloro-2-trifluoromethylaniline (**261h**) (139 mg, 71%) as a pale yellow oil. Spectroscopic data was consistent with the literature.[244] δ_H (500 MHz, $CDCl_3$) 4.17 (2H, br s, NH_2), 6.67 (1H, d, *J* 8.7 Hz, 6-H), 7.24 (1H, dd, *J* 8.7, 2.4 Hz, 5-H), 7.40 (1H, d, *J* 2.4 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 114.8 (C, q, $^2J_{CF}$ 30.8 Hz), 118.4 (CH), 122.4 (C), 124.1 (C, q, $^1J_{CF}$ 272.4 Hz), 126.3 (CH, q, $^3J_{CF}$ 5.5 Hz), 132.8 (CH), 143.1 (C); *m/z* (EI) 195 (M^+. 59%), 175 (45), 148 (36), 107 (19), 84 (100), 77 (46).

4-Amino-3-chlorobenzonitrile (261i)[245]



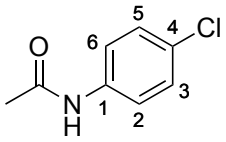
4-Amino-3-chlorobenzonitrile (**261i**) was synthesised as described for 4-chloroanisole (**261a**) using 4-aminobenzonitrile (118 mg, 1.00 mmol), iron(III) chloride (8.00 mg, 0.0500 mmol) and [BMIM]NTf_2 (44.0 μL, 0.150 mmol) in tetrahydrofuran (0.60 mL). The reaction was performed at 70 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 4-amino-3-chlorobenzonitrile (**261i**) (142 mg, 93%) as a white solid. Mp 102–104 °C (lit.[245] 106–108 °C); δ_H (400 MHz, $CDCl_3$) 4.65 (2H, br s, NH_2), 6.75 (1H, d, *J* 8.4 Hz, 5-H), 7.31 (1H, dd, *J* 8.4, 1.8 Hz, 6-H), 7.50 (1H, d, *J* 1.8 Hz, 2-H); δ_C (101 MHz, $CDCl_3$) 100.7 (C), 115.1 (CH), 118.5 (C), 119.0 (C), 132.0 (CH), 133.3 (CH), 147.2 (C); *m/z* (EI) 152 (M^+. 100%), 125 (45), 117 (46), 90 (47), 76 (40), 63 (45).

2-Chloro-4-nitroaniline (261j)[246]



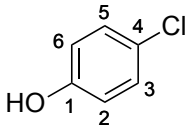
2-Chloro-4-nitroaniline (**261j**) was synthesised as described for 4-chloroanisole (**261a**) using 4-nitroaniline (138 mg, 1.00 mmol) and performing the reaction at 60 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 2-chloro-4-nitroaniline (**261j**) (153 mg, 89%) as a yellow solid. Mp 98–100 °C (lit.[246] 99–101 °C); δ_H (500 MHz, $CDCl_3$) 4.85 (2H, br s, NH_2), 6.75 (1H, d, *J* 8.9 Hz, 6-H), 7.98 (1H, dd, *J* 8.9, 2.5 Hz, 5-H), 8.19 (1H, d, *J* 2.5 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 113.7 (CH), 117.7 (C), 124.4 (CH), 126.0 (CH), 138.8 (C), 148.9 (C); *m/z* (EI) 172 (M^+. 100%), 142 (60), 126 (28), 99 (21), 90 (70), 63 (29).

4-Chloroacetanilide (261k)[247]



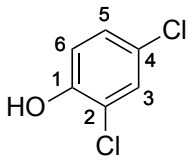
4-Chloroacetanilide (**261k**) was synthesised as described for 4-chloroanisole (**261a**) using acetanilide (135 mg, 1.00 mmol) and performing the reaction at 60 °C for 24 h. The reaction was performed as described in general procedure A using acetanilide (135 mg, 1.00 mmol). The reaction mixture was heated to 60 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave 4-chloroacetanilide (**261k**) (132 g, 78%) as a white solid. Mp 174–176 °C (lit.[247] 175–178 °C); δ_H (500 MHz, $CDCl_3$) 2.17 (3H, s, CH_3), 7.21–7.30 (3H, m, 3-H, 5-H and NH), 7.42–7.48 (2H, m, 2-H and 6-H); δ_C (126 MHz, $CDCl_3$) 24.6 (CH_3), 121.0 (2 × CH), 129.0 (2 × CH), 129.3 (C), 136.4 (C), 168.2 (C); *m/z* (ESI) 192 (MNa^+. 100%).

4-Chlorophenol (261l)[248]



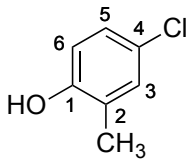
4-Chlorophenol (**261l**) was synthesised as described for 5-chloro-2,4-dimethoxybenzoic acid (**261d**) using phenol (94 mg, 1.0 mmol) and performing the reaction at 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chlorophenol (**261l**) (96 mg, 75%) as a colourless oil. Spectroscopic data was consistent with the literature.[248] δ_H (500 MHz, $CDCl_3$) 4.77 (1H, br s, OH), 6.74–6.79 (2H, m, 2-H and 6-H), 7.17–7.22 (2H, m, 3-H and 5-H); δ_C (126 MHz, $CDCl_3$) 116.7 (2 × CH), 125.7 (C), 129.5 (2 × CH), 154.0 (C); *m/z* (EI) 128 (M^+. 100%), 102 (34), 84 (90), 66 (98), 57 (27).

2,4-Dichlorophenol (256)[249]



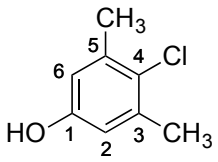
2,4-Dichlorophenol (**256**) was synthesised as described for 5-chloro-2,4-dimethoxybenzoic acid (**261d**) using phenol (94.0 mg, 1.00 mmol) and NCS (280 mg, 2.10 mmol) in tetrahydrofuran (1.20 mL). The reaction was performed at 60 °C for 48 h. Purification by flash column chromatography (petroleum ether/diethyl ether 19:1) gave 2,4-dichlorophenol (**256**) (131 mg, 81%) as a light orange solid. Mp 40–42 °C (lit.[249] 43–44 °C); δ_H (400 MHz, $CDCl_3$) 5.49 (1H, s, OH), 6.95 (1H, d, *J* 8.7 Hz, 6-H), 7.15 (1H, dd, *J* 8.7, 2.5 Hz, 5-H), 7.33 (1H, d, *J* 2.5 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 117.3 (CH), 120.6 (C), 125.8 (C), 128.7 (2 × CH), 150.4 (C); *m/z* (EI) 162 (M^+. 100%), 153 (21), 136 (18), 107 (46), 89 (38).

4-Chloro-2-methylphenol (261m)[250]



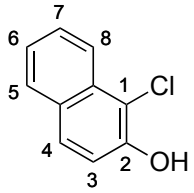
4-Chloro-2-methylphenol (**261m**) was synthesised as described for 5-chloro-2,4-dimethoxybenzoic acid (**261d**) using 2-methylphenol (108 mg, 1.00 mmol) and performing the reaction at 60 °C for 12 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chloro-2-methylphenol (**261m**) (115 mg, 81%) as a yellow solid. Mp 46–48 °C (lit.[250] 46–47 °C); δ_H (500 MHz, $CDCl_3$) 2.22 (3H, s, CH_3), 5.02 (1H, br s, OH), 6.69 (1H, d, *J* 8.5 Hz, 6-H), 7.03 (1H, dd, *J* 8.5, 2.7 Hz, 5-H), 7.10 (1H, d, *J* 2.7 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 15.7 (CH_3), 116.1 (CH), 125.3 (C), 125.8 (C), 126.8 (CH), 130.7 (CH), 152.3 (C); *m/z* (CI) 143 (MH^+. 48%), 113 (45), 97 (40), 85 (68), 71 (100), 69 (54).

4-Chloro-3,5-dimethylphenol (258)[251]



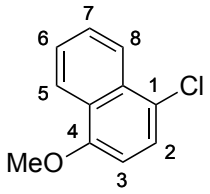
4-Chloro-3,5-dimethylphenol (**258**) was synthesised as described for 5-chloro-2,4-dimethoxybenzoic acid (**261d**) using 3,5-dimethylphenol (122 mg, 1.00 mmol) and performing the reaction at 60 °C for 12 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chloro-3,5-dimethylphenol (**258**) (119 mg, 76%) as a white solid. Mp 112–114 °C (lit.[251] 114–116 °C); δ_H (500 MHz, $CDCl_3$) 2.32 (6H, s, 2 × CH_3), 4.72 (1H, s, OH), 6.58 (2H, s, 2H and 6-H); δ_C (126 MHz, $CDCl_3$) 20.8 (2 × CH_3), 115.3 (2 × CH), 126.3 (C), 137.4 (2 × C), 153.2 (C); *m/z* (CI) 157 (MH^+. 26%), 113 (66), 97 (43), 85 (69), 71 (100), 69 (53).

1-Chloro-2-naphthol (261n)[252]



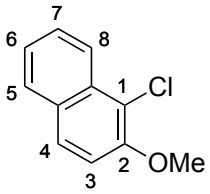
1-Chloro-2-naphthol (**261n**) was synthesised as described for 5-chloro-2,4-dimethoxybenzoic acid (**261d**) using 2-naphthol (144 mg, 1.00 mmol) and performing the reaction at 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 1-chloro-2-naphthol (**261n**) (174 mg, 97%) as an off-white solid. Mp 64–66 °C (lit.[252] 66 °C); δ_H (500 MHz, $CDCl_3$) 5.87 (1H, s, OH), 7.26 (1H, d, *J* 8.9 Hz, 3-H), 7.40 (1H, ddd, *J* 8.1, 6.8, 1.1 Hz, 6-H), 7.57 (1H, ddd, *J* 8.5, 6.8, 1.2 Hz, 7-H), 7.71 (1H, d, *J* 8.9 Hz, 4-H), 7.79 (1H, br d, *J* 8.1 Hz, 5-H), 8.06 (1H, br d, *J* 8.5 Hz, 8-H); δ_C (126 MHz, $CDCl_3$) 113.4 (C), 117.3 (CH), 122.8 (CH), 124.2 (CH), 127.6 (CH), 128.2 (CH), 128.5 (CH), 129.5 (C), 131.1 (C), 149.4 (C); *m/z* (ESI) 177 ($[M-H]^-$. 100%).

1-Chloro-4-methoxynaphthalene (261o)[253]



1-Chloro-4-methoxynaphthalene (**261o**) was synthesised as described for 4-chloroanisole (**261a**) using 1-methoxynaphthalene (144 μL, 1.00 mmol) and performing the reaction at 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-chloro-4-methoxynaphthalene (**261o**) (175 mg, 91%) as a colourless oil. Spectroscopic data was consistent with the literature.[253] δ_H (400 MHz, $CDCl_3$) 4.00 (3H, s, OCH_3), 6.73 (1H, d, *J* 8.3 Hz, 3-H), 7.46 (1H, d, *J* 8.3 Hz, 2-H), 7.54 (1H, ddd, *J* 8.3, 6.9, 1.3 Hz, 7-H), 7.62 (1H, ddd, *J* 8.4, 6.9, 1.4 Hz, 6-H), 8.20 (1H, br d, *J* 8.4 Hz, 5-H), 8.29 (1H, br d, *J* 8.3 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 55.7 (CH_3), 103.8 (CH), 122.4 (CH), 123.2 (C), 124.2 (CH), 125.7 (CH), 125.9 (CH), 126.6 (C), 127.5 (CH), 131.3 (C), 154.6 (C); *m/z* (EI) 192 (M^+. 100%), 177 (52), 149 (66), 114 (14), 84 (46).

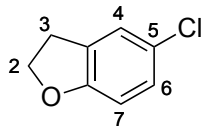
1-Chloro-2-methoxynaphthalene (261p)[254]



1-Chloro-2-methoxynaphthalene (**261p**) was synthesised as described for 4-chloroanisole (**261a**) using 2-methoxynaphthalene (158 mg, 1.00 mmol), iron(III) chloride (8.00 mg, 0.0500 mmol) and [BMIM]NTf2 (44.0 μL, 0.150 mmol). The reaction was performed at 70 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-chloro-2-methoxynaphthalene (**261p**) (173 mg, 90%) as a white solid. Mp 64–66 °C (lit.[254] 68–69 °C); δ_H (400 MHz, $CDCl_3$) 4.03 (3H, s, OCH_3), 7.29 (1H, d, *J* 9.0 Hz, 3-H), 7.41 (1H, ddd, *J* 8.2, 6.8, 1.2 Hz, 6-H), 7.58 (1H, ddd, *J* 8.4, 6.8, 1.2 Hz, 7-H), 7.77 (1H, d, *J* 9.0 Hz, 4-H), 7.80 (1H, br d, *J* 8.2 Hz, 5-H), 8.21–8.26 (1H, m, 8-H); δ_C (101 MHz, $CDCl_3$) 57.1 (CH_3), 113.8 (CH), 117.0 (C), 123.6 (CH), 124.4 (CH),

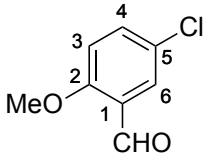
127.6 (CH), 128.1 (2 × CH), 129.6 (C), 132.0 (C), 152.7 (C); *m/z* (EI) 192 (M^+. 27%), 149 (25), 97 (18), 84 (91), 66 (100), 57 (43).

5-Chloro-2,3-dihydrobenzofuran (261q)[255]



5-Chloro-2,3-dihydrobenzofuran (**261q**) was synthesised as described for 4-chloroanisole (**261a**) using 2,3-dihydrobenzofuran (113 µL, 1.00 mmol) and performing the reaction at 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 5-chloro-2,3-dihydrobenzofuran (**261q**) (133 mg, 86%) as a colourless oil. Spectroscopic data was consistent with the literature.[255] δ_H (500 MHz, $CDCl_3$) 3.20 (2H, t, *J* 8.7 Hz, 3-H_2), 4.58 (2H, t, *J* 8.7 Hz, 2-H_2), 6.69 (1H, d, *J* 8.4 Hz, 7-H), 7.05 (1H, dd, *J* 8.4, 2.2 Hz, 6-H), 7.13–7.16 (1H, m, 4-H); δ_C (126 MHz, $CDCl_3$) 29.7 (CH_2), 71.6 (CH_2), 110.2 (CH), 124.9 (C), 125.0 (CH), 127.8 (CH), 128.9 (C), 158.7 (C); *m/z* (EI) 154 (M^+. 80%), 91 (41), 84 (100).

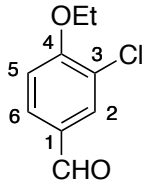
5-Chloro-2-methoxybenzaldehyde (261r)[256]



N-Chlorosuccinimide (62.0 mg, 0.460 mmol) was added to a solution of iron(III) chloride (3.70 mg, 0.0220 mmol) in [BMIM]NTf_2 (0.13 mL) under an atmosphere of air. The mixture was stirred at room temperature for 0.5 h before 2-methoxybenzaldehyde (60.0 mg, 0.440 mmol) in [BMIM]NTf_2 (0.05 mL) was added. The reaction mixture was heated to 70 °C for 18 h. The reaction progress was monitored by ^{1}H NMR spectroscopy. The reaction mixture was extracted into 5% ethyl acetate in hexane (3 × 30 mL) using sonication in a water bath for 0.1 h. The suspension was washed with an aqueous solution of 1 M sodium thiosulfate (7 mL), brine (7 mL), dried ($MgSO_4$) and then filtered through a pad of Celite®. The solvent was removed under reduced pressure. Purification by flash column

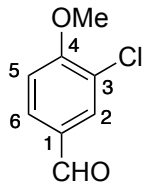
chromatography (petroleum ether/ethyl acetate, 9:1) gave 5-chloro-2-methoxybenzaldehyde (**261r**) (51.0 mg, 68%) as a white solid. Mp 78–79 °C (lit.[256] 80–81 °C); δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, OCH_3), 6.95 (1H, d, *J* 8.9 Hz, 3-H), 7.50 (1H, dd, *J* 8.9, 2.8 Hz, 4-H), 7.79 (1H, d, *J* 2.8 Hz, 6-H), 10.41 (1H, s, CHO); δ_C (126 MHz, $CDCl_3$) 56.0 (CH_3), 113.3 (CH), 125.7 (C), 126.4 (C), 128.0 (CH), 135.4 (CH), 160.3 (C), 188.5 (CH); *m/z* (EI) 170 (M^+. 17%), 153 (6), 84 (100), 49 (79), 44 (32).

3-Chloro-4-ethoxybenzaldehyde (261s)[257]



3-Chloro-4-ethoxybenzaldehyde (**261s**) was synthesised as described for 5-chloro-2-methoxybenzaldehyde (**261r**) using 4-ethoxybenzaldehyde (70 µL, 0.50 mmol) and performing the reaction at 70 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 17:3) gave 3-chloro-4-ethoxybenzaldehyde (**261s**) (65 mg, 70%) as a white solid. Mp 64–66 °C. Spectroscopic data was consistent with the literature.[257] δ_H (400 MHz, $CDCl_3$) 1.51 (3H, t, *J* 7.0 Hz, $OCH_2C\mathit{H}_3$), 4.19 (2H, q, *J* 7.0 Hz, $OC\mathit{H}_2CH_3$), 7.01 (1H, d, *J* 8.5 Hz, 5-H), 7.74 (1H, dd, *J* 8.5, 2.0 Hz, 6-H), 7.89 (1H, d, *J* 2.0 Hz, 2-H), 9.83 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 14.6 (CH_3), 65.3 (CH_2), 112.6 (CH), 124.0 (C), 130.2 (C), 130.6 (CH), 131.4 (CH), 159.5 (C), 189.8 (CH); *m/z* (EI) 184 (M^+. 15%), 157 (8), 153 (36), 136 (27), 124 (4), 107 (27), 84 (100), 77 (75), 63 (11), 51 (33).

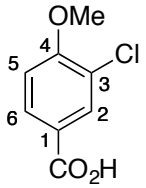
3-Chloro-4-methoxybenzaldehyde (261t)[258]



3-Chloro-4-methoxybenzaldehyde (**261t**) was synthesised as described for 5-chloro-2-methoxybenzaldehyde (**261r**) using 4-methoxybenzaldehyde (122 µL,

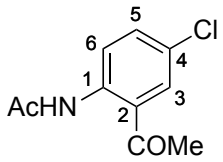
1.00 mmol) and NCS (160 mg, 1.20 mmol). The reaction was performed at 70 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate 19:1) gave 3-chloro-4-methoxybenzaldehyde (**261t**) (141 mg, 83%) as a pale yellow solid. Mp 52–54 °C (lit.[258] 53–55 °C); δ_H (400 MHz, $CDCl_3$) 3.99 (3H, s, OCH_3), 7.04 (1H, d, *J* 8.5 Hz, 5-H), 7.77 (1H, dd, *J* 8.5, 2.0 Hz, 6-H), 7.91 (1H, d, *J* 2.0 Hz, 2-H), 9.85 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 56.5 (CH_3), 111.7 (CH), 123.7 (C), 130.3 (C), 130.5 (CH), 131.2 (CH), 159.8 (C), 189.6 (CH); *m/z* (EI) 169 (M^+. 100%), 143 (13), 126 (15), 115 (19), 99 (14), 83 (16), 75 (12), 63 (26).

3-Chloro-4-methoxybenzoic acid (261u)[209]



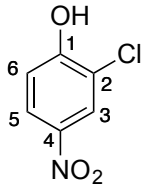
N-Chlorosuccinimide (70.0 mg, 0.525 mmol) was added to a solution of iron(III) chloride (4.00 mg, 0.0250 mmol) in [BMIM]NTf_2 (0.15 mL) under an atmosphere of air. The mixture was stirred at room temperature for 0.5 h before 4-methoxybenzoic acid (76.0 mg, 0.500 mmol) in [BMIM]NTf_2 (0.050 mL) was added. The reaction mixture was heated to 70 °C for 24 h. The reaction progress was monitored by ^{1}H NMR spectroscopy. The reaction mixture was diluted with dichloromethane (10 mL) and extracted with an aqueous solution of 1 M sodium hydroxide (5 mL). The aqueous phase was separated and then acidified with 1 M hydrochloric acid (5 mL), and extracted into dichloromethane (2 × 25 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 17:3) gave 3-chloro-4-methoxybenzoic acid (**261u**) (86.0 mg, 92%) as a white solid. Mp 208–210 °C (lit.[209] 211–214 °C); δ_H (400 MHz, $CDCl_3$) 3.99 (3H, s, OCH_3), 6.99 (1H, d, *J* 8.7 Hz, 5-H), 8.02 (1H, dd, *J* 8.7, 2.1 Hz, 6-H), 8.13 (1H, d, *J* 2.1 Hz, 2-H); δ_C (101 MHz, $CDCl_3$) 56.6 (CH_3), 111.5 (CH), 122.4 (C), 122.9 (C), 130.8 (CH), 132.5 (CH), 159.5 (C), 170.0 (C); *m/z* (EI) 186 (M^+. 83%), 169 (41), 115 (13), 83 (100), 63 (11).

N-(2-Acetyl-4-chlorophenyl)acetamide (261v)



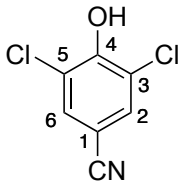
N-(2-Acetyl-4-chlorophenyl)acetamide (**261v**) was synthesised as described for 5-chloro-2-methoxybenzaldehyde (**261r**) using N-(2-acetylphenyl)acetamide (99.0 mg, 0.500 mmol) and performing the reaction at 70 °C for 48 h. Purification by flash column chromatography (petroleum ether/diethyl ether, 9:1) gave *N*-(2-acetyl-4-chlorophenyl)acetamide (**261v**) (101 mg, 95%) as a white solid. Mp 126–128 °C; ν_{max}/cm^{-1} (neat) 3218 (NH), 2359, 1685 (CO), 1657 (CO), 1588 (C=C), 1501, 1400, 1360, 1311, 1286, 1246, 1224, 828, 773, 637; δ_H (400 MHz, $CDCl_3$) 2.22 (3H, s, NHCOC*H*$_3$), 2.65 (3H, s, COCH_3), 7.49 (1H, dd, *J* 9.1, 2.5 Hz, 5-H), 7.82 (1H, d, *J* 2.5 Hz, 3-H), 8.72 (1H, d, *J* 9.1 Hz, 6-H), 11.56 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 25.6 (CH_3), 28.7 (CH_3), 122.4 (CH), 122.9 (C), 127.3 (C), 131.2 (CH), 135.0 (CH), 139.7 (C), 169.6 (C), 201.9 (C); *m/z* (EI) 211.0402 (M$^+$. $C_{10}H_{10}{}^{35}ClNO_2$ requires 211.0400), 169 (97), 154 (100).

2-Chloro-4-nitrophenol (255)[259]



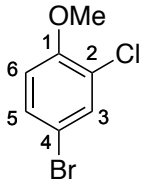
2-chloro-4-nitrophenol (**255**) was synthesised as described for 3-chloro-4-methoxybenzoic acid (**261u**) using 4-nitrophenol (70 mg, 0.50 mmol) and performing the reaction at 70 °C for 48 h. Purification by flash column chromatography (petroleum ether/ethyl acetate 3:1) gave 2-chloro-4-nitrophenol (**255**) (64 mg, 74%) as a yellow solid. Mp 108–110 °C (lit.[259] 110–112 °C); δ_H (400 MHz, $CDCl_3$) 6.34 (1H, s, OH), 7.13 (1H, d, *J* 9.0 Hz, 6-H), 8.12 (1H, dd, *J* 9.0, 2.7 Hz, 5-H), 8.29 (1H, d, *J* 2.7 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 116.4 (CH), 120.5 (C), 124.7 (CH), 125.5 (CH), 141.7 (C), 157.0 (C); *m/z* (EI) 173 (M$^+$. 100%), 143 (39), 107 (21), 99 (37), 84 (65), 63 (36).

3,5-Dichloro-4-hydroxybenzonitrile (259)



3,5-dichloro-4-hydroxybenzonitrile (**259**) was synthesised as described for 3-chloro-4-methoxybenzoic acid (**261u**) using 4-hydroxybenzonitrile (60.0 mg, 0.500 mmol) and NCS (147 mg, 1.10 mmol). The reaction was performed at 70 °C for 36 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 3,5-dichloro-4-hydroxybenzonitrile (**259**) (68.0 mg, 73%) as a white solid. Mp 128–130 °C; ν_{max}/cm^{-1} (neat) 3255 (OH), 2924 (CH), 2243 (CN), 1483, 1302, 1150, 909; δ_H (400 MHz, $CDCl_3$) 6.48 (1H, br s, OH), 7.59 (2H, s, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 105.4 (C), 116.7 (C), 122.3 (2 × C), 132.2 (2 × CH), 152.3 (C); *m/z* (EI) 186.9583 (M^+. $C_7H_3{}^{35}Cl_2NO$ requires 186.9592).

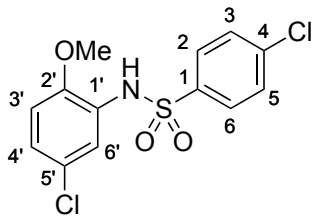
4-Bromo-2-chloroanisole (262)[260]



N-Bromosuccinimide (178 mg, 1.00 mmol) was added to a solution of iron(III) chloride (8.00 mg, 0.0500 mmol) in [BMIM]NTf_2 (0.400 mL) under an atmosphere of air. The mixture was stirred at room temperature for 0.5 h before anisole (108 µL, 1.00 mmol) in acetonitrile (0.10 mL) was added. The reaction mixture was heated to 40 °C for 1.5 h. The reaction mixture was cooled to room temperature and *N*-chlorosuccinimide (160 mg, 1.20 mmol) was then added. The reaction mixture was heated to 70 °C for 24 h. The reaction mixture was then extracted with 5% ethyl acetate in hexane (3 × 50 mL) using sonication in a water bath for 0.1 h. The suspension was washed with an aqueous solution of 1 M sodium thiosulfate (10 mL), brine (10 mL), dried ($MgSO_4$) and then filtered through a pad of Celite®. The solvent was removed under reduced pressure. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-bromo-2-

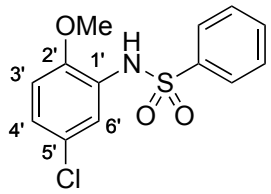
chloroanisole (**262**) (197 mg, 89%) as a pale yellow solid. Mp 66–68 °C (lit.[260] 66–68 °C); δ_H (400 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 6.79 (1H, d, *J* 8.8 Hz, 6-H), 7.33 (1H, dd, *J* 8.8, 2.4 Hz, 5-H), 7.50 (1H, d, *J* 2.4 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 56.3 (CH_3), 112.5 (C), 113.3 (CH), 123.7 (C), 130.5 (CH), 132.7 (CH), 154.4 (C); *m/z* (EI) 222 (M^+. 86%), 179 (100), 126 (36).

4-Chloro-*N*-(5'-chloro-2'-methoxyphenyl)benzenesulfonamide (263)[191]



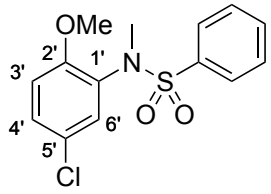
To a solution of 2-bromo-4-chloroanisole (**250d**) (110 mg, 0.500 mmol) in toluene (0.50 mL) were added 4-chlorobenzenesulfonamide (115 mg, 0.600 mmol), copper(I) iodide (10.0 mg, 0.0500 mmol), *N*,*N*′-dimethylethylenediamine (11.0 µL, 0.100 mmol), cesium carbonate (326 mg, 1.00 mmol) and water (0.30 mL). The reaction mixture was degassed under argon for 0.1 h and then heated to 150 °C for 24 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL), washed with 1 M sodium thiosulfate solution (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave 4-chloro-*N*-(5'-chloro-2'-methoxyphenyl)benzenesulfonamide (**263**) (107 mg, 65%) as a white solid. Mp 142–144 °C (lit.[191] 144–146 °C); δ_H (400 MHz, $CDCl_3$) 3.66 (3H, s, OCH_3), 6.67 (1H, d, *J* 8.7 Hz, 3'-H), 7.01 (1H, dd, *J* 8.7, 2.5 Hz, 4'-H), 7.03 (1H, br s, NH), 7.38–7.42 (2H, m, 3-H and 5-H), 7.53 (1H, d, *J* 2.5 Hz, 6'-H), 7.69–7.74 (2H, m, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 56.0 (CH_3), 111.6 (CH), 121.0 (CH), 125.3 (CH), 126.2 (C), 126.5 (C), 128.6 (2 × CH), 129.2 (2 × CH), 137.4 (C), 139.7 (C), 148.0 (C); *m/z* (EI) 331 (M^+. 100%), 296 (52), 262 (18), 158 (32), 156 (100), 126 (19), 111 (27), 93 (48), 75 (16).

***N*-(5'-Chloro-2'-methoxyphenyl)benzenesulfonamide (264)[187]**



The reaction was performed as described for 4-chloro-*N*-(5'-chloro-2'-methoxyphenyl)benzenesulfonamide (**263**) using 2-bromo-4-chloroanisole (**250d**) (221 mg, 1.00 mmol) and benzenesulfonamide (189 mg, 1.20 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-(5'-chloro-2'-methoxyphenyl)benzenesulfonamide (**264**) (199 mg, 67%) as a white solid. Mp 140–142 °C (lit.[187] 140–142 °C); δ_H (400 MHz, $CDCl_3$) 3.63 (3H, s, OCH_3), 6.64 (1H, d, *J* 8.7 Hz, 3'-H), 6.98 (1H, dd, *J* 8.7, 2.6 Hz, 4'-H), 7.02 (1H, br s, NH), 7.40–7.47 (2H, m, 2 × ArH), 7.50–7.53 (1H, m, ArH), 7.55 (1H, d, *J* 2.6 Hz, 6'-H), 7.76–7.82 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 56.0 (CH_3), 111.5 (CH), 120.8 (CH), 124.9 (CH), 126.1 (C), 126.9 (C), 127.2 (2 × CH), 128.9 (2 × CH), 133.1 (CH), 139.0 (C), 148.0 (C); *m/z* (EI) 297 (M^+. 79%), 156 (100), 93 (70), 77 (40), 51 (27).

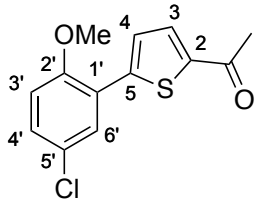
***N*-(5'-Chloro-2'-methoxyphenyl)-*N*-methylbenzenesulfonamide (260)[187]**



To a solution of *N*-(5'-chloro-2'-methoxyphenyl)benzenesulfonamide (**264**) (38 mg, 0.13 mmol) in DMF (0.7 mL) were added potassium carbonate (53 mg, 0.38 mmol) and iodomethane (24 µL, 0.38 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with water (2 mL) and extracted with diethyl ether (3 × 3 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave *N*-(5'-chloro-2'-methoxyphenyl)-*N*-methylbenzenesulfonamide (**260**) (37 mg, 93%) as a colourless oil. Spectroscopic data was consistent with the literature.[187] δ_H (500 MHz, $CDCl_3$)

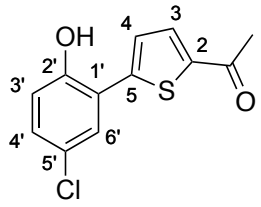
3.18 (3H, s, NCH_3), 3.36 (3H, s, OCH_3), 6.71 (1H, d, *J* 8.8 Hz, 3'-H), 7.23 (1H, dd, *J* 8.8, 2.7 Hz, 4'-H), 7.29 (1H, d, *J* 2.7 Hz, 6'-H), 7.44–7.50 (2H, m, 2 × ArH), 7.53–7.59 (1H, m, ArH), 7.66–7.71 (2H, m, 2 × ArH); δ_C (126 MHz, $CDCl_3$) 37.8 (CH_3), 55.3 (CH_3), 112.6 (CH), 125.1 (C), 127.5 (2 × CH), 128.6 (2 × CH), 129.4 (CH), 129.9 (C), 131.8 (CH), 132.4 (CH), 139.2 (C), 155.2 (C); *m/z* (EI) 311 (M^+. 41%), 170 (100), 155 (39), 84 (15), 77 (19).

2-(5-Acetylthien-2-yl)-4-chloroanisole (266)



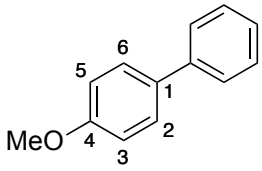
To a solution of 2-bromo-4-chloroanisole (**250d**) (160 mg, 0.730 mmol) in 1,4-dioxane (8 mL) were added 5-acetylthiophene-2-boronic acid (**265**) (148 mg, 0.870 mmol), potassium carbonate (303 mg, 2.19 mmol) and water (6.0 mL). The reaction mixture was degassed with argon for 0.1 h. Bis(triphenylphosphine)palladium(II) dichloride (51.0 mg, 0.0730 mmol) was added and the reaction mixture was heated to 80 °C for 4 h. The reaction mixture was cooled to room temperature and the organic solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (15 mL), extracted with water (10 mL) and washed with brine (10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 2-(5-acetylthien-2-yl)-4-chloroanisole (**266**) (154 mg, 79%) as a yellow solid. Mp 128–130 °C; ν_{max}/cm^{-1} 2941 (CH), 1653 (C=O), 1436, 1277, 1259, 1021, 807, 677; δ_H (500 MHz, $CDCl_3$) 2.57 (3H, s, $COCH_3$), 3.95 (3H, s, OCH_3), 6.93 (1H, d, *J* 8.8 Hz, 6-H), 7.27 (1H, dd, *J* 8.8, 2.6 Hz, 5-H), 7.47 (1H, d, *J* 4.1 Hz, 3'-H), 7.64–7.67 (2H, m, 3-H and 4'-H); δ_C (126 MHz, $CDCl_3$) 26.8 (CH_3), 55.9 (CH_3), 112.9 (CH), 123.6 (C), 126.0 (C), 126.2 (CH), 128.0 (CH), 129.3 (CH), 132.1 (CH), 143.8 (C), 146.1 (C), 154.6 (C), 191.1 (C); *m/z* (ESI) 289.0052 (MNa^+. $C_{13}H_{11}{}^{35}ClNaO_2S$ requires 289.0060).

2-(5-Acetylthien-2-yl)-4-chlorophenol (257)[182]



2-(5-Acetylthien-2-yl)-4-chloroanisole (**266**) (50.0 mg, 0.190 mmol) was dissolved in dichloromethane (3.0 mL) and cooled to −78 °C. Boron tribromide (374 µL, 0.370 mmol, 1 M in dichloromethane) was added dropwise and the reaction mixture was stirred at −78 °C for 1 h, before warming to room temperature over 5 h. The reaction mixture was quenched by the addition of a saturated solution of sodium bicarbonate (2 mL) and then extracted with dichloromethane (4 × 3 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave 2-(5-acetylthien-2-yl)-4-chlorophenol (**257**) (41.0 mg, 87%) as a yellow solid. Mp 212–214 °C (lit.[182] 218 °C); δ_H (500 MHz, DMSO-d_6) 2.53 (3H, s, $COCH_3$), 7.00 (1H, d, *J* 8.7 Hz, 6-H), 7.25 (1H, dd, *J* 8.7, 2.6 Hz, 5-H), 7.79 (1H, d, *J* 4.1 Hz, 3'-H), 7.84 (1H, d, *J* 2.6 Hz, 3-H), 7.89 (1H, d, *J* 4.1 Hz, 4'-H), 11.00 (1H, br s, OH); δ_C (126 MHz, DMSO-d_6) 27.0 (CH_3), 118.5 (CH), 121.7 (C), 123.7 (C), 126.7 (CH), 127.3 (CH), 129.8 (CH), 133.8 (CH), 143.5 (C), 146.0 (C), 153.4 (C), 191.5 (C); *m/z* (ESI) 251 ($[M-H]^-$. 100%).

4-Methoxybiphenyl (267)[261]



Iron(III) chloride (8.00 mg, 0.050 mmol), 1,3-bis-(2,6-diisopropylphenyl)imidazolinium chloride (SIPr.HCl) (64.0 mg, 0.150 mmol) and sodium *tert*-butoxide (17.0 mg, 0.180 mmol) were dissolved in THF (1.50 mL) and stirred at room temperature for 1 h, under an atmosphere of argon. To the solution, 4-chloroanisole (**261a**) (122 µL, 1.00 mmol) and phenylmagnesium bromide (2.00 mL, 2.00 mmol, 1 M in THF) were added and the reaction mixture

was stirred at 60 °C for 18 h. The reaction was quenched by addition of brine (10 mL) and then exacted with dichloromethane (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 18:2) gave 4-methoxybiphenyl (**267**) (148 mg, 80%) as a white solid. Mp 86–88 °C (lit.[261] 88–89 °C); δ_H (400 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 6.97–7.02 (2H, m, 3-H and 5-H), 7.29–7.34 (1H, m, ArH), 7.40–7.46 (2H, m, 2 × ArH), 7.52–7.59 (4H, m, 2-H, 6-H and 2 × ArH); δ_C (101 MHz, $CDCl_3$) 55.4 (CH_3), 114.3 (2 × CH), 126.7 (CH), 126.8 (2 × CH), 128.2 (2 × CH), 128.8 (2 × CH), 133.8 (C), 140.9 (C), 159.2 (C); *m/z* (EI) 184 (M^+. 100%), 169 (34), 167 (41), 141 (31).

4.0 References

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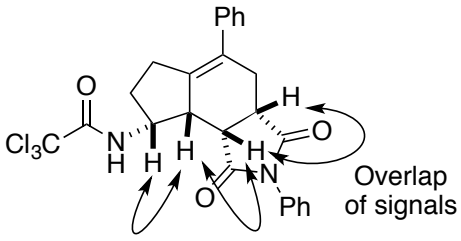
5.0 Appendices

Appendix 1: NOE data



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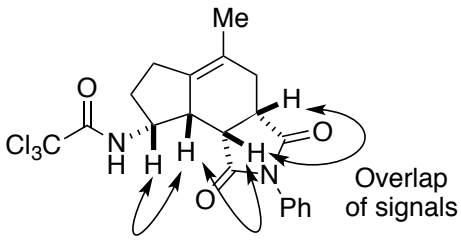

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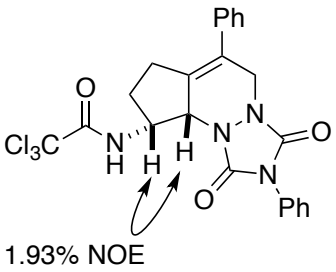

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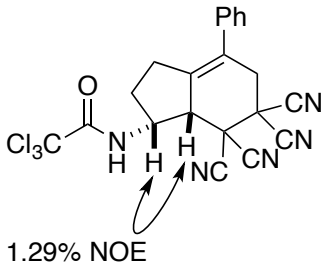

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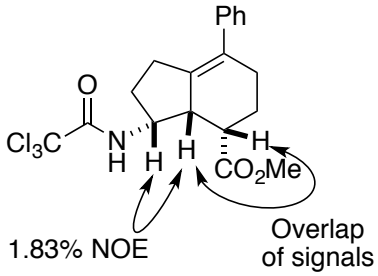

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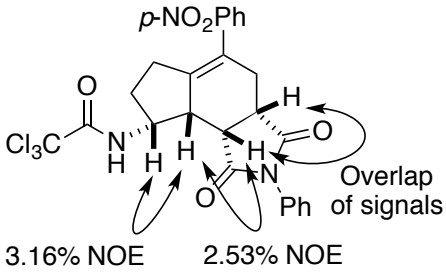

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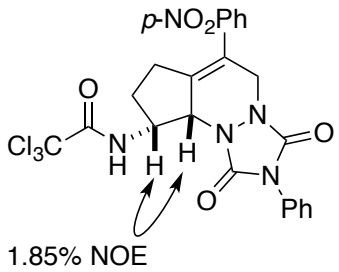

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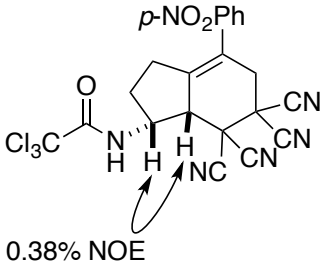

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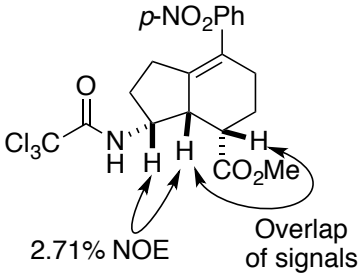

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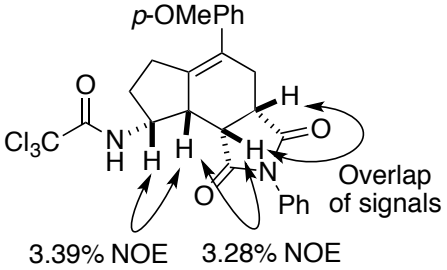

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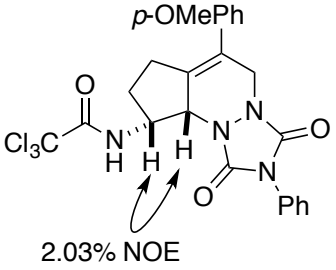

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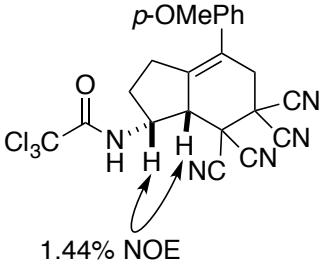

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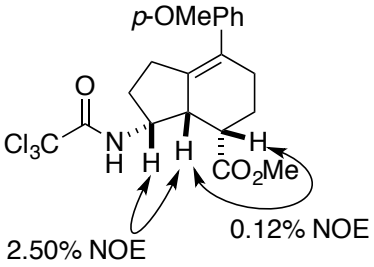

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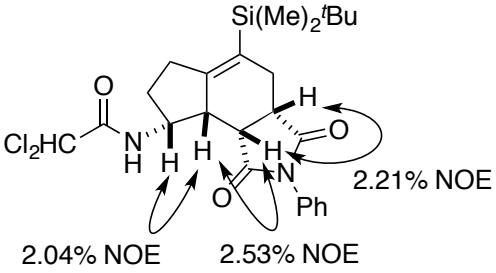

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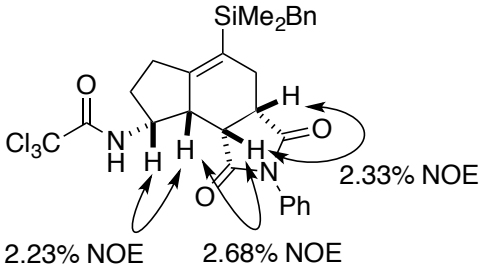

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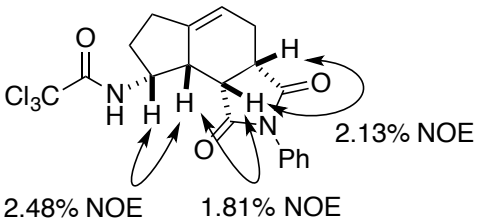

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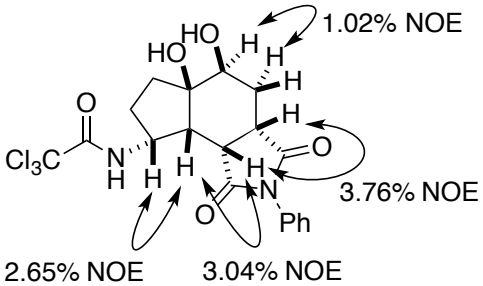

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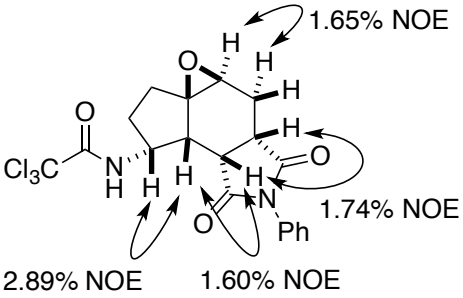

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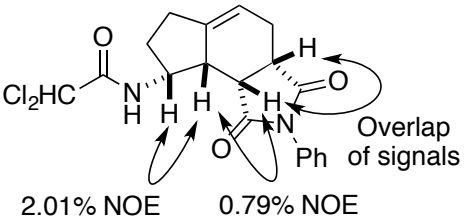

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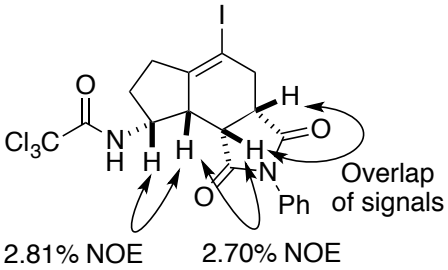

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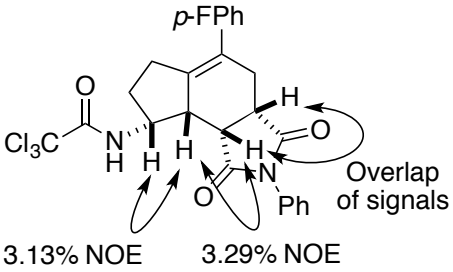

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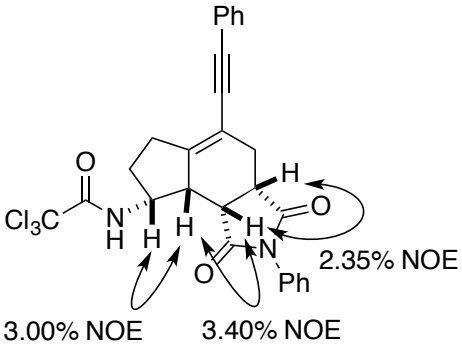
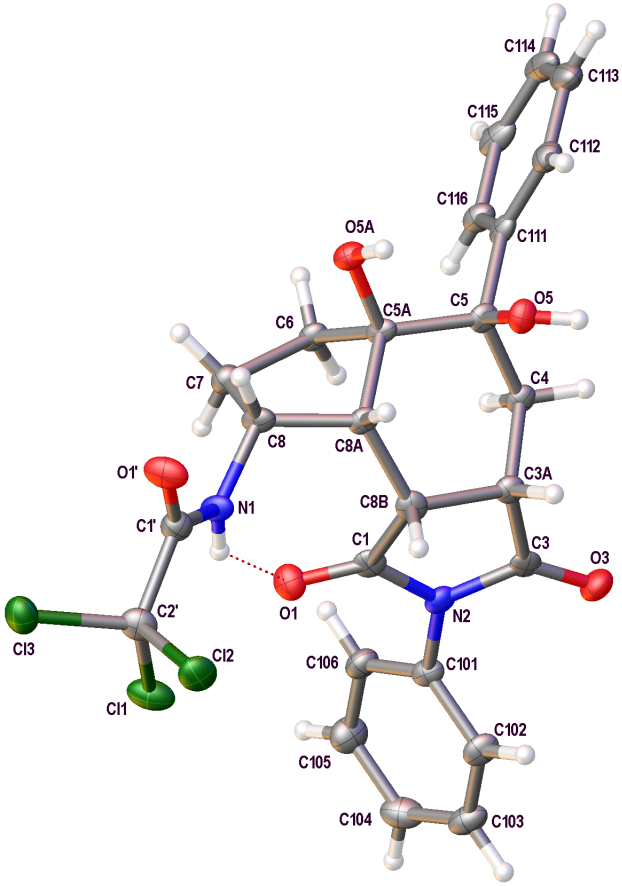


243

Appendix 2: X-ray data

Crystal data and structure refinement for 216



Identification code		**216**
Empirical formula		$C_{25}H_{23}Cl_3N_2O_5$
Formula weight		537.82
Temperature		100 K
Wavelength		0.71073 Å
Crystal system		Triclinic
Space group		P-1
Unit cell dimensions	*a* = 11.7084 (4) Å	α = 90.096 (3)°.
	b = 14.1127 (6) Å	β = 95.408 (3)°.
	c = 15.5928 (6) Å	γ = 91.971 (3)°.

Volume	2563.48 (17) $Å^3$
Z	4
Density (calculated)	1.477 Mg/m^3
Absorption coefficient	0.40 mm^{-1}
F(000)	1184
Theta range for data collection	4.4 to 50°
Index ranges −20<=l<=20	−15<=h<=15, −18<=k<=18,
Reflections collected	34139
Independent reflections	9008 [R_{int} = 0.073]
Completeness to theta = 25°	99.9%
Refinement method Full-matrix least-squares on F^2	0.054
Data / restraints / parameters	9008/ 0 /675
Goodness-of-fit on F2	1.01
Final R indices [I>2sigma(I)]	0.054 (6437)
R indices (all data)	0.136
Largest diff. peak and hole	0.42 and −0.37 e $Å^{-3}$

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	X	Y	Z	U_{iso}*/U_{eq}
Cl1	0.56318 (7)	0.41697 (6)	0.12159 (6)	0.0325 (2)
Cl2	0.70717 (7)	0.47561 (6)	–0.01123 (6)	0.0287 (2)
Cl3	0.50893 (7)	0.35127 (6)	–0.05247 (6)	0.0297 (2)
O1	0.69807 (18)	0.29606 (16)	0.28775 (14)	0.0239 (5)
O3	1.01209 (18)	0.36148 (16)	0.47674 (15)	0.0258 (5)
O5	1.13042 (17)	0.15698 (15)	0.23986 (13)	0.0205 (5)
H5	1.1885	0.1734	0.2705	0.031*
O1'	0.73834 (19)	0.26330 (16)	–0.02584 (14)	0.0289 (6)
O5A	0.95893 (17)	0.04964 (15)	0.15894 (13)	0.0202 (5)

H5A	1.0181	0.0677	0.1388	0.030*
N1	0.7174 (2)	0.26103 (18)	0.11762 (16)	0.0183 (6)
H1	0.6842	0.2876	0.1578	0.022*
N2	0.8391 (2)	0.33875 (18)	0.39405 (16)	0.0182 (6)
C1	0.7996 (3)	0.3039 (2)	0.3126 (2)	0.0193 (7)
C3	0.9585 (3)	0.3353 (2)	0.4103 (2)	0.0189 (7)
C4	1.0308 (3)	0.1850 (2)	0.3660 (2)	0.0178 (7)
H4A	1.1001	0.1879	0.4053	0.021*
H4B	0.9688	0.1600	0.3973	0.021*
C5	1.0477 (2)	0.1178 (2)	0.2918 (2)	0.0174 (7)
C6	0.8261 (2)	0.0702 (2)	0.2602 (2)	0.0181 (7)
H6A	0.8144	0.0957	0.3164	0.022*
H6B	0.8264	0.0016	0.2636	0.022*
C7	0.7318 (3)	0.1026 (2)	0.1911 (2)	0.0211 (7)
H7A	0.7042	0.0502	0.1535	0.025*
H7B	0.6674	0.1273	0.2180	0.025*
C8	0.7907 (3)	0.1812 (2)	0.1400 (2)	0.0200 (7)
H8	0.8100	0.1528	0.0860	0.024*
C101	0.7661 (3)	0.3812 (2)	0.4522 (2)	0.0188 (7)
C102	0.7950 (3)	0.4702 (2)	0.4852 (2)	0.0223 (8)
H102	0.8614	0.5023	0.4712	0.027*
C103	0.7239 (3)	0.5114 (2)	0.5395 (2)	0.0269 (8)
H103	0.7431	0.5713	0.5626	0.032*
C104	0.6256 (3)	0.4647 (2)	0.5595 (2)	0.0293 (8)
H104	0.5779	0.4930	0.5958	0.035*
C105	0.5969 (3)	0.3752 (3)	0.5258 (2)	0.0295 (8)
H105	0.5299	0.3436	0.5393	0.035*
C106	0.6679 (3)	0.3325 (2)	0.4721 (2)	0.0232 (8)
H106	0.6497	0.2721	0.4499	0.028*
C111	1.0837 (3)	0.0214 (2)	0.3272 (2)	0.0190 (7)
C112	1.1817 (3)	-0.0200 (2)	0.3024 (2)	0.0240 (8)
H112	1.2247	0.0110	0.2631	0.029*
C113	1.2160 (3)	–0.1064 (3)	0.3353 (2)	0.0311 (9)
H113	1.2816	–0.1329	0.3177	0.037*
C114	1.1542 (3)	–0.1535 (3)	0.3936 (2)	0.0341 (9)
H114	1.1782	–0.2113	0.4159	0.041*
C115	1.0558 (3)	–0.1141 (2)	0.4190 (2)	0.0288 (8)

H115	1.0127	–0.1461	0.4576	0.035*
C116	1.0221 (3)	–0.0275 (2)	0.3867 (2)	0.0215 (7)
H116	0.9568	–0.0010	0.4050	0.026*
C1'	0.6997 (3)	0.2943 (2)	0.0386 (2)	0.0218 (8)
C2'	0.6223 (3)	0.3815 (2)	0.0261 (2)	0.0241 (8)
C3A	1.0031 (2)	0.2852 (2)	0.33510 (19)	0.0175 (7)
H3A	1.0716	0.3185	0.3171	0.021*
C5A	0.9384 (2)	0.1102 (2)	0.22924 (19)	0.0160 (7)
C8A	0.9039 (2)	0.2080 (2)	0.19353 (19)	0.0168 (7)
H8A	0.9596	0.2279	0.1534	0.020*
C8B	0.9034 (2)	0.2871 (2)	0.2633 (2)	0.0192 (7)
H8B	0.9159	0.3464	0.2325	0.023*
Cl21	0.42396 (7)	0.06289 (6)	0.68326 (5)	0.0292 (2)
Cl22	0.28103 (7)	0.02545 (6)	0.52534 (6)	0.0287 (2)
Cl23	0.49942 (7)	0.12707 (6)	0.52317 (6)	0.0306 (2)
O21	0.30895 (18)	0.20125 (17)	0.83235 (14)	0.0268 (6)
O23	–0.00657 (18)	0.13584 (16)	0.97481 (14)	0.0264 (5)
O25	–0.12130 (17)	0.34204 (16)	0.72273 (14)	0.0230 (5)
H25	–0.1794	0.3257	0.7451	0.035*
O21'	0.2880 (2)	0.24170 (17)	0.51339 (15)	0.0296 (6)
O25A	0.04980 (17)	0.44734 (15)	0.66487 (13)	0.0217 (5)
H25A	–0.0108	0.4300	0.6378	0.033*
N21	0.2894 (2)	0.23331 (18)	0.65891 (16)	0.0204 (6)
H21	0.3166	0.2034	0.7039	0.025*
N22	0.1672 (2)	0.15851 (18)	0.91785 (16)	0.0198 (6)
C21	0.2079 (3)	0.1937 (2)	0.8427 (2)	0.0202 (7)
C23	0.0471 (3)	0.1623 (2)	0.9161 (2)	0.0218 (7)
C24	–0.0212 (3)	0.3136 (2)	0.8627 (2)	0.0192 (7)
H24A	–0.0900	0.3115	0.8928	0.023*
H24B	0.0417	0.3379	0.9025	0.023*
C25	–0.0381 (3)	0.3812 (2)	0.7868 (2)	0.0186 (7)
C26	0.1845 (2)	0.4278 (2)	0.7844 (2)	0.0198 (7)
H26A	0.1965	0.4034	0.8426	0.024*
H26B	0.1851	0.4965	0.7870	0.024*
C27	0.2779 (3)	0.3938 (2)	0.7290 (2)	0.0235 (8)
H27A	0.3421	0.3692	0.7651	0.028*
H27B	0.3059	0.4455	0.6948	0.028*

C28	0.2185 (3)	0.3147 (2)	0.6701 (2)	0.0204 (7)
H28	0.1993	0.3422	0.6131	0.024*
C201	0.2390 (3)	0.1156 (2)	0.9859 (2)	0.0213 (7)
C202	0.2108 (3)	0.0255 (2)	1.0127 (2)	0.0251 (8)
H202	0.1442	–0.0059	0.9887	0.030*
C203	0.2822 (3)	–0.0181 (3)	1.0756 (2)	0.0334 (9)
H203	0.2629	–0.0785	1.0946	0.040*
C204	0.3816 (3)	0.0281 (3)	1.1098 (3)	0.0430 (10)
H204	0.4311	–0.0018	1.1505	0.052*
C205	0.4076 (3)	0.1193 (3)	1.0833 (3)	0.0473 (11)
H205	0.4740	0.1510	1.1073	0.057*
C206	0.3363 (3)	0.1636 (3)	1.0218 (2)	0.0358 (9)
H206	0.3536	0.2251	1.0047	0.043*
C211	–0.0742 (3)	0.4776 (2)	0.8173 (2)	0.0195 (7)
C212	–0.1736 (3)	0.5178 (2)	0.7803 (2)	0.0276 (8)
H212	–0.2168	0.4869	0.7348	0.033*
C213	–0.2093 (3)	0.6034 (3)	0.8104 (2)	0.0344 (9)
H213	–0.2765	0.6290	0.7854	0.041*
C214	–0.1464 (3)	0.6506 (3)	0.8768 (2)	0.0361 (10)
H214	–0.1707	0.7079	0.8967	0.043*
C215	–0.0461 (3)	0.6122 (2)	0.9141 (2)	0.0320 (9)
H215	–0.0023	0.6444	0.9585	0.038*
C216	–0.0114 (3)	0.5259 (2)	0.8851 (2)	0.0245 (8)
H216	0.0548	0.4999	0.9114	0.029*
C21'	0.3136 (3)	0.2037 (2)	0.5818 (2)	0.0203 (7)
C22'	0.3774 (3)	0.1090 (2)	0.5805 (2)	0.0211 (7)
C23A	0.0046 (3)	0.2129 (2)	0.8353 (2)	0.0193 (7)
H23A	–0.0644	0.1806	0.8070	0.023*
C25A	0.0713 (3)	0.3882 (2)	0.73877 (19)	0.0182 (7)
C28A	0.1047 (3)	0.2891 (2)	0.7085 (2)	0.0181 (7)
H28A	0.0485	0.2693	0.6607	0.022*
C28B	0.1047 (2)	0.2105 (2)	0.7781 (2)	0.0194 (7)
H28B	0.0922	0.1510	0.7455	0.023*
O1M	0.31816 (19)	0.2291 (2)	0.33926 (15)	0.0357 (6)
H1M	0.3227	0.2289	0.3921	0.053*
C1M	0.4282 (3)	0.2283 (4)	0.3119 (3)	0.0593 (14)
H1MA	0.4231	0.2312	0.2501	0.089*

H1MB	0.4645	0.1711	0.3309	0.089*
H1MC	0.4727	0.2821	0.3357	0.089*
O2M	–0.30712 (19)	0.26944 (19)	0.79678 (15)	0.0322 (6)
H2M	–0.3069	0.2802	0.8485	0.048*
C2M	–0.4126 (3)	0.2935 (3)	0.7546 (3)	0.0466 (11)
H2MA	–0.4734	0.2590	0.7794	0.070*
H2MB	–0.4144	0.2777	0.6946	0.070*
H2MC	–0.4225	0.3603	0.7608	0.070*

Bond-length (Å) for 216

Cl1–C2'	1.778 (3)	O25–H25	0.8200
Cl2–C2'	1.764 (3)	O25–C25	1.425 (4)
Cl3–C2'	1.760 (3)	O21'–C21'	1.212 (4)
O1–C1	1.216 (4)	O25A–H25A	0.8200
O3–C3	1.210 (4)	O25A–C25A	1.432 (4)
O5–H5	0.8200	N21–H21	0.8600
O5–C5	1.419 (3)	N21–C28	1.460 (4)
O1'–C1'	1.226 (4)	N21–C21'	1.331 (4)
O5A–H5A	0.8200	N22–C21	1.393 (4)
O5A–C5A	1.432 (3)	N22–C23	1.407 (4)
N1–H1	0.8600	N22–C201	1.438 (4)
N1–C8	1.463 (4)	C21–C28B	1.524 (4)
N1–C1'	1.320 (4)	C23–C23A	1.501 (5)
N2–C1	1.393 (4)	C24–H24A	0.9700
N2–C3	1.400 (4)	C24–H24B	0.9700
N2–C101	1.445 (4)	C24–C25	1.524 (4)
C1–C8B	1.523 (4)	C24–C23A	1.532 (4)
C3–C3A	1.512 (4)	C25–C211	1.527 (4)
C4–H4A	0.9700	C25–C25A	1.543 (4)
C4–H4B	0.9700	C26–H26A	0.9700
C4–C5	1.526 (4)	C26–H26B	0.9700
C4–C3A	1.530 (4)	C26–C27	1.545 (4)
C5–C111	1.526 (4)	C26–C25A	1.532 (4)
C5–C5A	1.535 (4)	C27–H27A	0.9700
C6–H6A	0.9700	C27–H27B	0.9700
C6–H6B	0.9700	C27–C28	1.548 (4)
C6–C7	1.550 (4)	C28–H28	0.9800

C6–C5A	1.533 (4)	C28–C28A	1.543 (4)
C7–H7A	0.9700	C201–C202	1.378 (5)
C7–H7B	0.9700	C201–C206	1.377 (5)
C7–C8	1.547 (4)	C202–H202	0.9300
C8–H8	0.9800	C202–C203	1.386 (5)
C8–C8A	1.533 (4)	C203–H203	0.9300
C101–C102	1.377 (4)	C203–C204	1.377 (5)
C101–C106	1.379 (4)	C204–H204	0.9300
C102–H102	0.9300	C204–C205	1.386 (6)
C102–C103	1.382 (4)	C205–H205	0.9300
C103–H103	0.9300	C205–C206	1.376 (5)
C103–C104	1.369 (5)	C206–H206	0.9300
C104–H104	0.9300	C211–C212	1.389 (5)
C104–C105	1.386 (5)	C211–C216	1.393 (5)
C105–H105	0.9300	C212–H212	0.9300
C105–C106	1.385 (4)	C212–C213	1.388 (5)
C106–H106	0.9300	C213–H213	0.9300
C111–C112	1.391 (4)	C213–C214	1.369 (5)
C111–C116	1.398 (4)	C214–H214	0.9300
C112–H112	0.9300	C214–C215	1.388 (5)
C112–C113	1.382 (5)	C215–H215	0.9300
C113–H113	0.9300	C215–C216	1.385 (5)
C113–C114	1.373 (5)	C216–H216	0.9300
C114–H114	0.9300	C21'–C22'	1.554 (4)
C114–C115	1.386 (5)	C23A–H23A	0.9800
C115–H115	0.9300	C23A–C28B	1.540 (4)
C115–C116	1.379 (5)	C25A–C28A	1.550 (4)
C116–H116	0.9300	C28A–H28A	0.9800
C1'–C2'	1.555 (4)	C28A–C28B	1.553 (4)
C3A–H3A	0.9800	C28B–H28B	0.9800
C3A–C8B	1.540 (4)	O1M–H1M	0.8200
C5A–C8A	1.542 (4)	O1M–C1M	1.396 (4)
C8A–H8A	0.9800	C1M–H1MA	0.9600
C8A–C8B	1.558 (4)	C1M–H1MB	0.9600
C8B–H8B	0.9800	C1M–H1MC	0.9600
Cl21–C22'	1.775 (3)	O2M–H2M	0.8200
Cl22–C22'	1.768 (3)	O2M–C2M	1.396 (4)

Cl23–C22'	1.766 (3)	C2M–H2MA	0.9600
O21–C21	1.210 (4)	C2M–H2MB	0.9600
O23–C23	1.211 (4)	C2M–H2MC	0.9600

Bond Angle (°) for 216

C5–O5–H5	109.5	C23–N22–C201	124.0 (3)
C5A–O5A—H5A	109.5	O21–C21–N22	123.2 (3)
C8–N1–H1	118.5	O21–C21–C28B	128.8 (3)
C1'–N1–H1	118.5	N22–C21–C28B	107.9 (3)
C1'–N1–C8	123.1 (3)	O23–C23–N22	123.5 (3)
C1–N2–C3	112.4 (3)	O23–C23–C23A	128.5 (3)
C1–N2–C101	123.7 (3)	N22–C23–C23A	107.7 (3)
C3–N2–C101	123.7 (3)	H24A–C24–H24B	107.8
O1–C1–N2	122.7 (3)	C25–C24–H24A	109.0
O1–C1–C8B	129.1 (3)	C25–C24–H24B	109.0
N2–C1–C8B	108.1 (3)	C25–C24–C23A	112.8 (3)
O3–C3–N2	124.3 (3)	C23A–C24–H24A	109.0
O3–C3–C3A	127.7 (3)	C23A–C24–H24B	109.0
N2–C3–C3A	107.8 (3)	O25–C25–C24	110.2 (3)
H4A–C4–H4B	107.8	O25–C25–C211	110.8 (3)
C5–C4–H4A	109.1	O25–C25–C25A	102.5 (2)
C5–C4–H4B	109.1	C24–C25–C211	110.2 (2)
C5–C4–C3A	112.5 (3)	C24–C25–C25A	110.3 (3)
C3A–C4–H4A	109.1	C211–C25–C25A	112.6 (3)
C3A–C4–H4B	109.1	H26A–C26–H26B	108.9
O5–C5–C4	110.3 (2)	C27–C26–H26A	110.8
O5–C5–C111	110.9 (2)	C27–C26–H26B	110.8
O5–C5–C5A	103.0 (2)	C25A–C26–H26A	110.8
C4–C5–C111	109.9 (3)	C25A–C26–H26B	110.8
C4–C5–C5A	110.3 (2)	C25A–C26–C27	104.7 (2)
C111–C5–C5A	112.2 (2)	C26–C27–H27A	110.7
H6A–C6–H6B	108.9	C26–C27–H27B	110.7
C7–C6–H6A	110.9	C26–C27–C28	105.4 (2)
C7—C6—H6B	110.9	H27A–C27–H27B	108.8
C5A–C6–H6A	110.9	C28–C27–H27A	110.7
C5A–C6–H6B	110.9	C28–C27–H27B	110.7
C5A–C6–C7	104.3 (2)	N21–C28–C27	114.2 (2)

C6–C7–H7A	110.7	N21–C28–H28	107.6
C6–C7–H7B	110.7	N21–C28–C28A	113.8 (3)
H7A–C7–H7B	108.8	C27–C28–H28	107.6
C8–C7–C6	105.1 (2)	C28A–C28–C27	105.7 (2)
C8–C7–H7A	110.7	C28A–C28–H28	107.6
C8–C7–H7B	110.7	C202–C201–N22	119.3 (3)
N1–C8–C7	113.5 (2)	C206–C201–N22	119.9 (3)
N1–C8–H8	107.5	C206–C201–C202	120.9 (3)
N1–C8–C8A	114.6 (2)	C201–C202–H202	120.2
C7–C8–H8	107.5	C201–C202–C203	119.7 (3)
C8A–C8–C7	106.0 (2)	C203–C202–H202	120.2
C8A–C8–H8	107.5	C202–C203–H203	120.0
C102–C101–N2	119.2 (3)	C204–C203–C202	119.9 (4)
C102–C101–C106	121.3 (3)	C204–C203–H203	120.0
C106–C101–N2	119.4 (3)	C203–C204–H204	120.2
C101–C102–H102	120.4	C203–C204–C205	119.6 (4)
C101–C102–C103	119.1 (3)	C205–C204–H204	120.2
C103–C102–H102	120.4	C204–C205–H205	119.6
C102–C103–H103	119.8	C206–C205–C204	120.7 (4)
C104–C103–C102	120.5 (3)	C206–C205–H205	119.6
C104–C103–H103	119.8	C201–C206–H206	120.4
C103–C104–H104	120.0	C205–C206–C201	119.1 (4)
C103–C104–C105	120.1 (3)	C205–C206–H206	120.4
C105–C104–H104	120.0	C212–C211–C25	120.7 (3)
C104–C105–H105	119.9	C212–C211–C216	118.0 (3)
C106–C105–C104	120.1 (3)	C216–C211–C25	121.2 (3)
C106–C105–H105	119.9	C211–C212–H212	119.6
C101–C106–C105	118.9 (3)	C213–C212–C211	120.8 (3)
C101–C106–H106	120.6	C213–C212–H212	119.6
C105–C106–H106	120.6	C212–C213–H213	119.7
C112–C111–C5	120.6 (3)	C214–C213–C212	120.6 (4)
C112–C111–C116	117.5 (3)	C214–C213–H213	119.7
C116–C111–C5	121.9 (3)	C213–C214–H214	120.2
C111–C112–H112	119.5	C213–C214–C215	119.6 (3)
C113–C112–C111	121.0 (3)	C215–C214–H214	120.2
C113–C112–H112	119.5	C214–C215–H215	120.0
C112–C113–H113	119.6	C216–C215–C214	119.9 (3)

C114–C113–C112	120.7 (3)	C216–C215–H215	120.0
C114–C113–H113	119.6	C211–C216–H216	119.5
C113–C114–H114	120.3	C215–C216–C211	121.0 (3)
C113–C114–C115	119.5 (3)	C215–C216–H216	119.5
C115–C114–H114	120.3	O21'–C21'–N21	126.4 (3)
C114–C115–H115	120.1	O21'–C21'–C22'	117.7 (3)
C116–C115–C114	119.9 (3)	N21–C21'–C22'	115.8 (3)
C116–C115–H115	120.1	Cl22–C22'–Cl21	108.81 (18)
C111–C116–H116	119.3	Cl23–C22'–Cl21	107.90 (17)
C115–C116–C111	121.5 (3)	Cl23–C22'–Cl22	109.80 (17)
C115–C116–H116	119.3	C21'–C22'–Cl21	115.3 (2)
O1'–C1'–N1	126.5 (3)	C21'–C22'–Cl22	106.6 (2)
O1'–C1'–C2'	116.9 (3)	C21'–C22'–Cl23	108.4 (2)
N1–C1'–C2'	116.6 (3)	C23–C23A–C24	106.3 (2)
Cl2–C2'–Cl1	109.67 (18)	C23–C23A–H23A	111.0
Cl3–C2'–Cl1	108.61 (17)	C23–C23A–C28B	104.6 (2)
Cl3–C2'–Cl2	109.79 (18)	C24–C23A–H23A	111.0
C1'–C2'–Cl1	113.7 (2)	C24–C23A–C28B	112.7 (3)
C1'–C2'–Cl2	107.3 (2)	C28B–C23A–H23A	111.0
C1'–C2'–Cl3	107.7 (2)	O25A–C25A–C25	108.7 (2)
C3–C3A–C4	106.3 (2)	O25A–C25A–C26	104.8 (2)
C3–C3A–H3A	110.9	O25A–C25A–C28A	108.8 (2)
C3–C3A–C8B	104.4 (2)	C25–C25A–C28A	111.0 (2)
C4–C3A–H3A	110.9	C26–C25A–C25	120.5 (2)
C4–C3A–C8B	113.2 (2)	C26–C25A–C28A	102.4 (2)
C8B–C3A–H3A	110.9	C28–C28A–C25A	100.6 (2)
O5A–C5A–C5	108.7 (2)	C28–C28A–H28A	107.4
O5A–C5A–C6	104.4 (2)	C28–C28A–C28B	118.3 (3)
O5A–C5A–C8A	108.9 (2)	C25A–C28A–H28A	107.4
C5–C5A–C8A	111.5 (2)	C25A–C28A–C28B	115.0 (2)
C6–C5A–C5	120.1 (3)	C28B–C28A–H28A	107.4
C6–C5A–C8A	102.6 (2)	C21–C28B–C23A	103.0 (2)
C8–C8A–C5A	100.6 (2)	C21–C28B–C28A	122.7 (3)
C8–C8A–H8A	107.6	C21–C28B–H28B	104.9
C8–C8A–C8B	118.3 (2)	C23A–C28B–C28A	114.9 (3)
C5A–C8A–H8A	107.6	C23A–C28B–H28B	104.9
C5A–C8A–C8B	114.4 (2)	C28A–C28B–H28B	104.9

C8B–C8A–H8A	107.6	C1M–O1M–H1M	109.5
C1–C8B–C3A	103.1 (2)	O1M–C1M–H1MA	109.5
C1–C8B–C8A	122.6 (3)	O1M–C1M–H1MB	109.5
C1–C8B–H8B	104.8	O1M–C1M–H1MC	109.5
C3A–C8B–C8A	115.0 (2)	H1MA–C1M–H1MB	109.5
C3A–C8B–H8B	104.8	H1MA–C1M–H1MC	109.5
C8A–C8B–H8B	104.8	H1MB–C1M–H1MC	109.5
C25–O25–H25	109.5	C2M–O2M–H2M	109.5
C25A–O25A–H25A	109.5	O2M–C2M–H2MA	109.5
C28–N21–H21	118.7	O2M–C2M–H2MB	109.5
C21'–N21–H21	118.7	O2M–C2M–H2MC	109.5
C21'–N21–C28	122.6 (3)	H2MA–C2M–H2MB	109.5
C21–N22–C23	112.3 (3)	H2MA–C2M–H2MC	109.5
C21–N22–C201	123.5 (3)	H2MB–C2M–H2MC	109.5

Atomic displacement parameters ($Å^2 \times 10^3$) for 216

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl1	45.6 (5)	29.5 (5)	25.2 (5)	15.3 (4)	12.1 (4)	9.8 (4)
Cl2	33.4 (4)	20.8 (5)	32.3 (5)	–2.4 (4)	5.2 (4)	9.8 (4)
Cl3	28.4 (4)	29.6 (5)	30.0 (5)	0.5 (4)	–2.4 (4)	8.4 (4)
O1	25.8 (12)	30.7 (14)	15.1 (12)	1.3 (10)	1.7 (10)	5.2 (10)
O3	33.0 (12)	22.1 (13)	21.2 (14)	–1.7 (10)	–1.9 (11)	–3.9 (11)
O5	22.1 (11)	22.9 (13)	16.0 (12)	–4.9 (10)	1.8 (9)	4.4 (10)
O1'	42.8 (14)	28.6 (14)	17.1 (13)	13.2 (11)	7.2 (11)	10.0 (11)
O5A	29.0 (12)	17.6 (12)	14.1 (12)	0.9 (10)	2.2 (10)	1.0 (10)
N1	29.7 (14)	15.1 (14)	10.2 (14)	4.7 (11)	0.3 (11)	4.9 (11)
N2	25.6 (14)	13.0 (14)	15.8 (15)	–3.0 (11)	2.2 (11)	2.2 (11)
C1	29.0 (18)	12.1 (17)	16.9 (18)	–0.2 (14)	2.6 (14)	8.7 (14)
C3	25.2 (16)	9.1 (16)	22.0 (2)	–1.7 (13)	1.9 (15)	6.7 (14)
C4	24.3 (16)	13.8 (17)	15.0 (17)	–2.9 (13)	1.8 (13)	3.9 (13)
C5	21.4 (15)	15.1 (17)	15.9 (18)	–4.1 (13)	4.5 (13)	4.9 (14)
C6	25.8 (16)	13.6 (17)	14.4 (17)	–2.3 (13)	0.0 (14)	4.7 (14)
C7	26.4 (17)	17.8 (18)	18.5 (18)	–1.0 (14)	0.2 (14)	1.8 (14)
C8	31.0 (17)	14.5 (17)	14.6 (18)	5.0 (14)	0.7 (14)	4.7 (14)
C101	28.4 (17)	16.5 (18)	11.5 (17)	1.5 (14)	1.9 (14)	3.3 (14)
C102	33.6 (18)	16.7 (18)	16.9 (18)	–5.1 (15)	5.0 (15)	5.2 (14)

C103	44.0 (2)	18.0 (19)	18.8 (19)	0.8 (16)	2.0 (16)	0.3 (15)
C104	43.0 (2)	29.0 (2)	18.3 (19)	11.0 (17)	9.2 (16)	4.2 (16)
C105	31.2 (18)	29.0 (2)	29.0 (2)	–3.9 (16)	8.9 (16)	1.9 (17)
C106	30.6 (18)	16.9 (18)	21.4 (19)	–2.6 (14)	0.8 (15)	0.7 (15)
C111	28.1 (17)	16.3 (18)	10.8 (17)	–3.9 (14)	–6.0 (13)	0.8 (14)
C112	28.3 (17)	22.1 (19)	20.7 (19)	–2.1 (15)	–1.8 (15)	–4.5 (15)
C113	37.0 (2)	24.0 (2)	31.0 (2)	6.2 (16)	–10.5 (17)	–7.8 (17)
C114	54.0 (2)	19.0 (2)	25.0 (2)	6.5 (18)	–22.2 (18)	–0.9 (17)
C115	52.0 (2)	20.0 (2)	12.7 (18)	–6.6 (17)	–7.0 (16)	2.4 (15)
C116	31.8 (18)	16.6 (18)	15.4 (18)	–0.9 (14)	–1.4 (14)	1.9 (14)
C1'	24.5 (17)	19.2 (19)	0.022 (2)	–0.1 (14)	2.3 (15)	3.1 (15)
C2'	30.6 (18)	23.0 (19)	19.5 (19)	3.1 (15)	5.6 (15)	8.7 (15)
C3A	21.7 (16)	14.6 (17)	16.2 (18)	–1.9 (13)	3.8 (13)	4.7 (14)
C5A	26.6 (16)	12.3 (16)	9.0 (16)	1.3 (13)	1.5 (13)	3.2 (13)
C8A	24.1 (16)	13.4 (17)	12.8 (17)	–2.1 (13)	2.9 (13)	3.5 (13)
C8B	23.8 (16)	17.0 (18)	17.3 (18)	–1.9 (13)	4.4 (14)	8.3 (14)
Cl21	39.0 (5)	23.8 (5)	24.2 (5)	5.1 (4)	–0.9 (4)	7.4 (4)
Cl22	31.3 (4)	24.8 (5)	29.6 (5)	–2.9 (4)	1.9 (4)	–5.7 (4)
Cl23	30.0 (4)	24.2 (5)	40.1 (6)	2.6 (4)	15.4 (4)	6.1 (4)
O21	24.9 (12)	38.2 (15)	17.3 (13)	–0.3 (11)	2.6 (10)	6.8 (11)
O23	35.2 (13)	21.3 (13)	23.9 (14)	–1.2 (10)	10.1 (11)	8.5 (11)
O25	24.2 (12)	27.8 (14)	16.8 (12)	–2.4 (10)	1.6 (10)	0.4 (11)
O21'	46.7 (14)	30.2 (14)	13.3 (13)	16.2 (12)	4.9 (11)	4.9 (11)
O25A	29.4 (12)	21.5 (13)	14.1 (12)	–0.3 (10)	1.2 (10)	6.7 (10)
N21	28.9 (14)	21.0 (15)	11.8 (15)	4.0 (12)	2.7 (11)	3.4 (12)
N22	27.8 (14)	19.8 (15)	11.6 (14)	–2.8 (12)	1.7 (11)	2.8 (12)
C21	29.9 (18)	15.7 (18)	14.9 (18)	–0.4 (14)	1.8 (14)	0.4 (14)
C23	34.9 (18)	9.0 (17)	21.9 (19)	–2.5 (14)	6.5 (16)	–1.8 (14)
C24	24.6 (16)	17.0 (18)	16.4 (18)	–1.8 (14)	5.0 (14)	4.8 (14)
C25	25.7 (16)	15.9 (17)	13.2 (17)	–3.3 (14)	–1.0 (14)	2.4 (14)
C26	27.7 (17)	15.4 (17)	15.8 (18)	–3.8 (14)	1.1 (14)	1.0 (14)
C27	29.5 (17)	21.0 (19)	20.5 (19)	1.1 (15)	4.7 (15)	2.2 (15)
C28	29.4 (17)	18.6 (18)	13.6 (17)	2.9 (14)	3.8 (14)	2.3 (14)
C201	7.4 (17)	24.5 (19)	11.4 (17)	–3.0 (15)	–0.4 (14)	3.6 (14)
C202	37.4 (19)	20.4 (19)	17.7 (19)	0.3 (15)	3.5 (15)	0.0 (15)
C203	49.0 (2)	30.0 (2)	21.0 (2)	1.6 (18)	2.4 (17)	10.9 (17)
C204	49.0 (2)	51.0 (3)	27.0 (2)	1.0 (2)	–7.7 (19)	18.0 (2)

C205	44.0 (2)	63.0 (3)	30.0 (2)	–16.0 (2)	–13.8 (19)	19.0 (2)
C206	44.0 (2)	37.0 (2)	24.0 (2)	–14.4 (18)	–5.8 (17)	12.7 (18)
C211	29.6 (17)	17.1 (18)	12.4 (18)	–3.5 (14)	6.6 (14)	3.8 (14)
C212	35.3 (19)	23.0 (2)	26.0 (2)	2.0 (16)	9.2 (16)	9.3 (16)
C213	42.0 (2)	24.0 (2)	40.0 (2)	8.4 (17)	17.5 (19)	14.5 (19)
C214	59.0 (2)	18.0 (2)	37.0 (2)	1.9 (18)	32.0 (2)	5.3 (18)
C215	61.0 (2)	16.1 (19)	22.0 (2)	–7.8 (18)	20.0 (18)	2.9 (16)
C216	38.6 (19)	19.9 (19)	16.6 (19)	0.3 (15)	11.4 (15)	6.8 (15)
C21'	22.8 (16)	19.4 (18)	18.9 (19)	1.3 (14)	1.7 (14)	2.5 (15)
C22'	26.1 (16)	20.8 (19)	16.1 (18)	–2.2 (14)	1.3 (14)	5.5 (14)
C23A	24.0 (16)	16.5 (18)	17.1 (18)	–5.0 (13)	2.0 (14)	2.1 (14)
C25A	26.4 (16)	18.0 (18)	10.1 (17)	1.3 (14)	1.2 (13)	1.6 (14)
C28A	24.3 (16)	17.6 (18)	11.8 (17)	–2.1 (13)	0.0 (13)	–0.3 (14)
C28B	25.6 (16)	13.4 (17)	18.5 (18)	–3.8 (13)	1.1 (14)	–0.2 (14)
O1M	30.2 (13)	58.6 (18)	17.7 (14)	–9.4 (12)	3.3 (10)	0.9 (14)
C1M	38.0 (2)	110.0 (4)	31.0 (3)	11.0 (2)	4.6 (19)	15.0 (3)
O2M	32.8 (13)	44.2 (16)	19.8 (14)	–1.5 (12)	4.8 (11)	–0.1 (12)
C2M	43.0 (2)	64.0 (3)	32.0 (2)	2.0 (2)	0.3 (19)	–1.0 (2)